Review Article

Implant - Controlled Release Medicated Formulation

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ABSTRACT
The implants are the most common and efficient for the delivery of active drug substance with good bioavailability and with narrow therapeutic index. The implant offers rapid and control on set of action with rapid declines of systemic drug deliver. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It available in the various dosage forms like tablet, capsule, injection, chip, patches, pump, with effective treatment lead to patient comfort for this reason implant deliver system which can uses as per patient requirement in various dosage forms with effective treatment to improve patient complains. These implants delivery system offer attractive opportunities for protein delivery & could possibly extend patient life of protein containing implant. This article explores various control release implantable drug delivery system & there strategies of preparation, their potential benefits/ drawbacks. Development of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated; Treatment of anterior-segment diseases has witnessed advances in prod rug formulations and permeability enhancers.

Keywords: Implant Pump, Dental treatment, Chip, Ion and cochlear Implant.

INTRODUCTION

An ideal controlled release drug delivery system is the one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time[1].

Implants are controlled release devices that can provide a larger depot of the therapeutic agent. They are intended for the controlled release of the therapeutic agent over relatively longer periods of time- several days to years. Implants are typically administered by an invasive procedure. Three dimensional implants may be as small as a few millimeters or a few centimeters. Greater therapeutic efficacy of the drug can also be achieved by such delivery systems when compared to conventional oral or IV formulation. More selective a drug to its site of action, the lesser the dose of the drug to be administered[1].

TYPE

1. **Biodegradable:**
   Biodegradable polymers are highly desirable for drug delivery applications because the devise will disappear over time, thereby eliminating the need for a second surgical procedure to retrieve the devise. The ZOLADEX implant is a sterile, biodegradable product containing goserelin acetate equivalent to 10.8mg. Now a day it's widely use in matrix to prepare membrane [1].
2. **Non-biodegradable:**
   The release kinetics of drugs from non-biodegradable implant systems depends on both the solubility and diffusion coefficient of the drug in the polymer and the drug load. A disadvantage of this system is that a minor surgery is required for the removal of delivery system from the body[1].
3. **Pump systems:**

Pump systems provide external control of delivery rate and volume. Controlled release of drug from an implantable pump is generally achieved by utilizing the micro technology of electronic systems and remote-controlled flow rate manipulation by maintaining a constant pressure difference. Ex. Infusion pumps, osmotic pump[1].

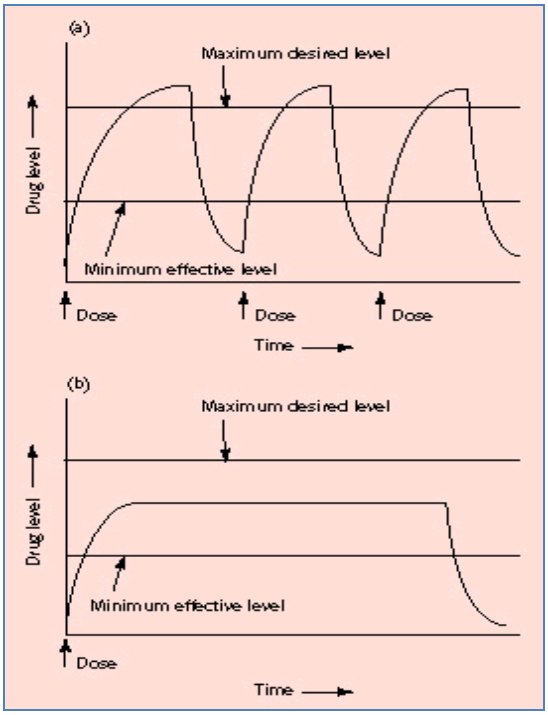

Fig. 1: Conventional Vs Implant drug release

Fig. 2: Chip Implant[6]

IMPLANTS AND PROCEDURES

Clavicle or collarbone piercing:

A very deep piercing that passes beneath the collarbone. Therefore enters the body cavity. These are highly prone to rejection as the collarbone placement is a high movement area. Also with the piercing going so deep under the collarbone and through that much flesh and muscle it is a hard to heal piercing. With all the movement in the area the fistula cannot heal properly. It will hurt far worse than a hip piercing [3].

Deep chest piercing:

A deep chest piercing is a long piercing that passes under the skin of the chest and may be several inches long[2].

Eyeball Implant:

An eyeball implant, or extra ocular implant is a cosmetic implant involving a tiny piece of decorative jewelry which is implanted within the superficial, interpalpebral conjunctiva of the human eye. Such implants are illegal in the United States, and are currently available only in the Netherlands[3].

Flesh stapling, flesh plating and pocketing:

A flesh staple is a type of piercing jewellery or implant in which the middle, rather than the end of the jewellery is exposed when worn. The jewellery resembles a staple, the ends of which pierce the skin and hold the item in place. Flesh pocketing achieves a similar effect to flesh stapling and plating, but with a lower rate of success.

Genital beading and genital ribs:

Genital beading (also known as yakuza beads, love beads or pearling) is a process in which beads or other small objects are implanted beneath the shaft skin of the penis, or into the labia. Genital ribs are short, slightly curved rods of various materials such as stainless steel, titanium, Teflon, or silicone placed under the shaft skin of the penis[4].

Horn Implants:

In this modification, small pieces of Teflon or silicone are inserted beneath the skin of the forehead, giving the appearance of small horns. These can be gradually replaced with larger and larger pieces as the skin stretch, creating larger horns. The first set of horn implants were done by Steve Haworth on The Enigma. Steve Haworth invented this type of modification. He currently uses silicone for his horn implants [4].

Magnetic Implants:

An experimental procedure in which small neodymium magnets are placed under the skin (usually the fingertips) mostly for the purpose sensory experimentation, in which the movement of the implant in the presence of magnetic fields can be felt by the individual.[9] Such implants can, in this way, be employed to convert non-human sensory information, such as sonar/distance, into touch. They have been proposed to be used to attach things such as eyeglasses or jewelry to the skin, but in practice this has turned out not to be feasible, as the skin is damaged by being crushed against the magnet[4].

Scrotal Implant:

A scrotal implant is an implant placed into the scrotum. The implants may be designed for this purpose (for example, Nautical), or be of any implant-grade material.

Subdermal Implant:

Subdermal implants, objects inserted under the skin, are used in medical applications such as pacemakers and the Norplant contraceptive. There is also historical evidence that some tribal cultures would insert stones or metal underneath the skin for ritualistic purposes. In the early 90's, body modification artist Steve Haworth conceived of inserting 3D art implants in various shapes under the skin to create a decorative appearance. He started with surgical steel and moved on to Teflon and then carved silicone, and now uses injection-molded implant-grade silicone that he produces. Other artists have since manufactured silicone implants using water jet cutting or "cookie cutter", but these often have undesirably sharp edges which can damage the skin.

Subdermal implants are usually installed by creating a hole in the skin which is expanded to allow insertion of the object, and then sutured closed. Magnets and RFID transmitters have also been implanted in humans using this method[3].

Surface piercing:

A surface piercing is a piercing that travels beneath the surface of the skin (on the arm, for example) rather than through a protruding portion of the anatomy such as the earlobe. Surface piercings can be placed on nearly any area of the body, provided they are not subject to too much movement or the risk of impact damage or infection from contact with contaminants such as dirt. A surface piercing should be done with high grade titanium in a staple shaped bar. Curved barbells or straight barbells put too much pressure on the entry holes for them to be suitable. Once a surface piercing bar is in it is recommended that you do not attempt to remove or change the staple shaped bar yourself & a highly trained & experienced piercer should do it. The balls however are all right to be changed[8].

Transdermal Implant:

A transdermal implant (or percutaneous implant), also known as a microdermal implant or surface anchor, is an implant incorporating a flat plate that sits beneath the skin with an externally visible portion incorporating a bead, spike or other item that appears to float on the surface of the skin. Due to the fact that the skin is held open by the metal and fistula must form around it, similar to a piercing on a larger scale, healing can sometimes be difficult or lengthy. If the practitioner is skilled and the person receiving the modification takes good care of it, it can have a high success rate. The first transdermal implant was a "Metal Mohawk" performed on Joe Aylward by Steve Haworth in 1996. Aylward retained his transdermal "mohawk" for almost a decade, until, for personal reasons, he requested to have Haworth remove it[9].

Absorbable Implants:
Implants constructed of materials designed to be absorbed by the body without producing an immune response. They are usually composed of plastics and are frequently used in orthopedics and orthodontics.

Prostheses and Implants:
Artificial substitutes for body parts, and materials inserted into tissue for functional, cosmetic, or therapeutic purposes. Prostheses can be functional, as in the case of artificial arms and legs, or cosmetic, as in the case of an artificial eye. Implants, all surgically inserted or grafted into the body, tend to be used therapeutically. IMPLANTS, EXPERIMENTAL is available for those used experimentally[5].

Breast Implants:
Implants used to reconstruct and/or cosmetically enhance the female breast. They have an outer shell or envelope of silicone elastomer and are filled with either saline or silicone gel. The outer shell may be either smooth or textured.

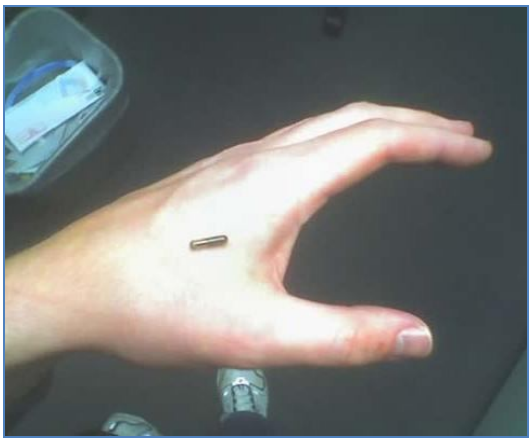

Fig. 3: Capsule Implant

Fig. 4: Microchip

METHOD OF PREPARATION

1. Encapsulating medicament in polymeric cell or capsule:
   Silicon capsule or silicon tubes are used. The suitable tubes are cut into specific site & they are most thoroughly in hot solution of amine soap. Then tubes are placed in pyrogen free Distill water and dried at 65˚ C. one end of the tube is sealed by silicon adhesive. A fixed quantity of drug or drug solution is filled by syringe in to capsule.

2. Fabrication of matrix type polymeric devise:
   In this system the drug reservoir is prepared by homogenously dispersing drug particles a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer, by the cross-linking of liner polymer chains.

ADVANTAGES

1. Fewer side effects.
2. Immediate termination of drug therapy in case of emergencies or toxicity.
3. Site specific drug delivery lowers the dose to be administered, thereby minimizing the side effect.
4. Greater therapeutic efficacy of drug that also be achieved by such delivery system.
5. For controlled release of therapeutic agent over relatively longer periods of time.
6. Hormonal replacement therapy.

DISADVANTAGES

1. A minor surgery is required at the site of Implantation.
2. Cause of drug dumping.
3. Dose adjustment is not possible.
4. Higher cost of therapy.

APPLICATIONS

1. Hormone replacement therapy.
2. Widely use in contraceptive.
3. Insulin for diabetes.
4. Pilocarpine for glaucoma.
5. Occurcert ophthalmic.

MARKETED PREPRATION[10]

Drug	Commercial name	Company
Resperidone	Risperdal® Constra®	Janseen®/Alkermes,Inc
Naltrexone	Vivitrol®	Alkermes
Leuprolide	Lupron Depot® Enantone Depot® Trenantone® Enantone Gyn	TAP Takeda Takeda Takeda
Octreotide	Sandostatin®LAR	Novartis
Somatotropin	Nutropin®Depot	Genentech/ Alkermes
Triptrorelin	Trelstar™Depot	Pfizer
Buserelin	Suprecur®MP	Sanofi-Aventis

EVALUTION PARAMETERS

1. **In-Vitro and In-Vivo release profile:**

In-Vitro evaluation Studies:

Release studies for each of the implant designs (n = 6 for each) were conducted in isotonic phosphate buffer (5 mm; pH 7.4). Implants were placed in 8-mL glass vials filled with the buffer and incubated in a shaking water bath at 37°C. At predetermined time intervals, the solution in the vial was removed and replenished. The sample was filtered through a 0.22 µm filter and analyzed using the fluoro spectrophotometric method[11].

Analytical Instrument and Methods:

For the in vitro release samples, EE_2 was analyzed using a fluorospectrophotometer at an excitation wavelength of 288 nm and emission wavelength of 311 nm. A standard curve was established before each quantitative analysis. Residual drug content was analyzed using a high performance liquid chromatography (HPLC) method. A rapid, sensitive HPLC method for determining EE_2 content in the implants was developed. A Hewlett-Packard 1100 HPLC device was used. The active component was separated from excipients on reverse-phase C8 column (Alltech, Lichrosorb RP-8, 5 m, 4.6 × 250 mm) by elution with water-acetonitrile (40:60) at a flow rate of 1 ml/min. An ultraviolet detector set at 280 nm was used. The samples were extracted with dioxane and diluted with mobile phase. The detection limit was 1 µg/ml[12].

In-Vivo Evaluations:

Ovariectomized Rabbit Model:

Twelve female New Zealand White rabbits, surgically ovariectomized, were purchased from Covance Research Products Inc (Denver, PA). All animals were recovered after the surgery for at least 3 weeks before the initiation of studies. The animals were housed individually in cages under environmentally controlled conditions (temperature 20°C ± 1°C, relative humidity 50%, and a 12-hour lighting cycle). These animals were fed once daily with a standard rabbit diet that is commercially available and had access to water ad libitum. The ovariectomized rabbit model was used to simulate actual postmenopausal conditions, in which natural estradiol production is suppressed[13-14].

Animal Study:

On the day of implantation, the procedure was carried out as described elsewhere. In brief, the hair over the lower lumbar dorsal site of each rabbit was clipped and the skin was cleaned by alcohol swab. Before implant insertion, the animals were anesthetized by subcutaneous injection of lidocaine and all apparatus and tools were sterilized. After placing each EE_2 implant inside a 10-gauge hypodermic needle, the needle was introduced, in parallel with the

vertebral column, into the subdermal tissue. The EE_2 implant was then gently pushed through the needle into the subdermal tissue while the needle was withdrawn and the implant was left inside the subdermal tissue. A piece of Band-Aid was then applied over the insertion site to prevent infection[15].

Following the implantation, serial blood samples (~4 ml each) were drawn from the rabbits' marginal veins at 1, 2, 4, 7, 10, 14, 18, 22, 26, and 30 days and once a week thereafter for a total of 13 weeks. The blood samples were centrifuged, and plasma was immediately transferred into a vacuum tube containing NaF and then stored in a freezer at -20°C until assay of EE_2, estradiol (E_2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) was completed. A capillary GC/MS-method, using negative ion chemical ionization with selective ion monitoring, was used to determine the plasma concentrations of EE_2, while specific radioimmunoassays (RIAs) were used to determine the plasma levels of E_2, FSH, and LH. Three prototypes of EE_2 implants were administered randomly into 3 groups of rabbits (4 rabbits in each group). A total of 12 experiments were performed. The mean body weight of rabbits was ~2.5 kg at time of implantation and ~3.5 kg at completion of the 13-week implantation studies[17].

2. **Dimension of devise (Implant)**:

One Dimensional (long channel) analysis:

The substrate doping profile for the 40 keV, 6.7 10 atoms/cm channel implant incident on the 350-°a gate oxide, is shown in Fig. 5. Since the oxide absorbs 3 percent of the incident dose, the active dose in the silicon is 6.5 10 atoms/cm. The concentration at the time of the implantation is given by the lightly dashed Gaussian function added to the background doping level, For 40 keV B ions, the projected range and standard deviation were taken as 1300 °A and 500 A^0, respectively[18]. After the heat treatments of the subsequent processing, the boron is redistributed as shown by the heavier dashed line. These predicted profiles were obtained using a computer program developed by F. F. Morehead of our laboratories. The program assumes that boron atoms diffusing in the silicon reflect from the silicon-oxide interface and thereby raise the surface concentration. The step profile approximates the final predicted profile rather well and offers the advantage that it can be described by a few simple parameters The three profiles shown in Fig. 5 all have the same active dose. Using the step profile, a model for determining threshold voltage has been developed from piecewise solutions of Poisson's equation with appropriate boundary conditions[19]. The one-dimensional model considers only the vertical dimension and cannot account for horizontal short-channel effects.

Two dimensional (short channel) analyses:

For devices with sufficiently short-channel lengths, the one-dimensional model is inadequate to account for the threshold voltage lowering due to penetration of the drain field into the channel region normally controlled by the gate. While some models have been developed which account for this behavior [20], the problem is complicated for the ion-implanted structure by the non-uniform doping profile which leads to an electric field pattern that is difficult to approximate. For the ion-implanted case, the two-dimensional numerical current transport model of Kennedy and Mock [21, 22] was utilized. The computer program was modified by W. Chang and P. Hwang [23] to handle the abrupt substrate doping profiles considered for these devices.

CONCLUSION

Implant drug delivery system having long duration of action in no. of months and

year as compare to other system. In case of toxicity it is easily remove from the site of implant. Therefore it is more preferable in long time disease condition.

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