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IMPLANTABLE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Recently Implantable drug delivery is one of the technology sectors that often overlooked in the development of new drug delivery by the formulation, research and development in any pharmaceuticals. Implant drug delivery technologies have ability to reduce the frequency of patient drive dosing and to deliver the compound in targeted manner. Implantable drug delivery systems are an example of such system available for therapeutic use. The study currently available implantable drug delivery system is the main focus of the review. Some of the most recently discovered implants are in the early developmental stages and more rigorous clinical testing is required prior to their use in standard practice. Implantable technologies, material science, data management, and biology science have significantly developed in recent years providing a multidisciplinary foundation for developing integrated therapeutic system. If small scale biosensor and drug reservoir units are combined and implanted, a wireless integrated system can regulate drug release, receive sensor feedback and transmit updates.

INTRODUCTION

Orally administered drug must be protected against denaturation in the gastrointestinal tract and should be capable of absorption across the wall of the stomach or the intestine. The rate of the drug absorption and elimination should ensure the blood levels within the therapeutic range oral controlled release dosage forms can provide efficacy for about 24 hours. The main drawback of oral dosage forms is the long transit time of approximately 12 hours through the gastrointestinal tract (GIT). If drug cannot be administered orally, A parenteral route or implantable route of delivery is an alternative.(1)

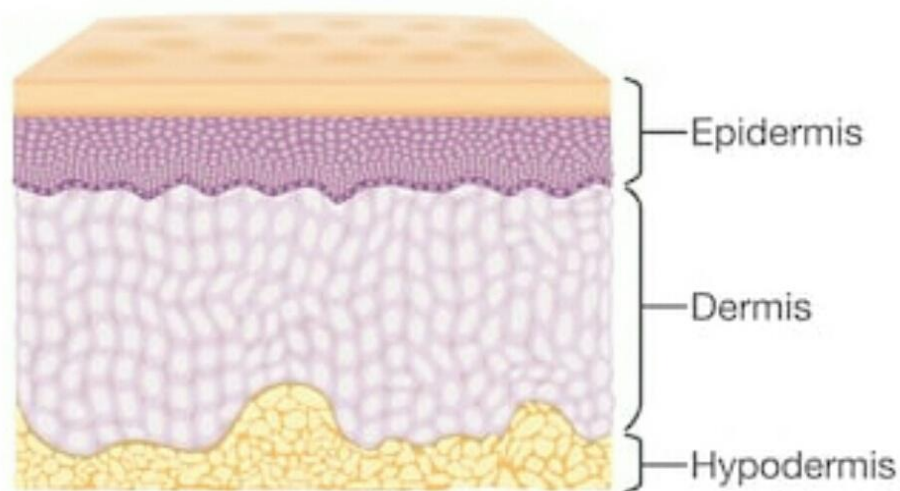


Fig no: 1.1

Devoid of aforementioned limitations associated with oral, IV, topical drug administration. Implant is a single unit drug that has been designed to deliver a drug moiety at a therapeutically desired rate over a prolonged period of time. Intended for implantation subcutaneously in the body for continuous release of drug over extended period of time.(2)

Subcutaneously or under the skin and the human skin and the human skin is the outer covering of the body. In human, it is the largest organ the integumentary system The integumentary system helps to maintain a constant body temperature, protects the body and provides sensory information about the surrounding environment. It consist of two main parts is epidermis and dermis. Epidermis is the outermost layer of skin. It is composed of keratinized stratified squamous epithelium. Dermis is the second deeper layer of the skin dermis. It is composed of mainly connective tissue the function of subcutaneously is the

sensation are sensation that arise in the skin including touch, pressure, vibration and tickling.(3)

The concept of implantable drug delivery system in modern medicine may be stress to deans by and parks that, in 1938, subcutaneously implanted compress pellets are crystalline estrogen. Folk man and long pioneered implantable formulation with drug release pets controlled by a polymeric membrane in the 1960s. They investigated the use of silicon rubber form long term drug delivery at a systemic level. from this early beginning, the potential of this mode of delivery in a overcoming problems associated with oral administration, such as drug bioavailability, stability, toxicity and duration of release, was recognized.(4)

Implant delivery systems have been subsequently designed to reduce the frequently of dosing, prolong duration of action, increased the patient compliance, and reduce the systematic side effects. implantable drug delivery system are very attractive for a number of classes of drug, particularly those that cannot be delivered via the oral route, are irregularly absorbed via the gastrointestinal tract, or that benefit from site specific dosing. example include steroids, chemotherapeutic, antibiotic, analgesic, and contraceptives and biologics such as insulin or heparin.(5)

Implant morphology is typically cylindrical with monolithic device at the millimeter or centimeter scale being most commonly employ in addition to subcutaneous implantation, various other body regions have also successfully served as implantation sites, particularly for delivery to localized tissue such as intra-vaginal, intravascular, intraocular, intra-theal, intracranial and peritoneal perhaps the most common clinical application to data target cardiac or carotid arteries as site for drug -eluting stents (DES), delivering therapy to intravascular locations.(6)

Implants can be use as delivering system for either systemic or local therapeutics effects for systemic therapeutic effects, implants are typically administered sc, intramuscularly or intravenously , were by the incorporated drug is delivered from the implant and absorbed into the blood circulation. Implants for local effects are place into specific body sites where the drug acts local, with relatively negligible absorption into the systemic circulation.(7)

More recently many excellent ex. of micro-needle patches employing both passive and active models of drug delivery have been develop. however, as these micro-needle have a relatively minimal portion of the total device penetrating the skin often transient bases, they cannot be classically define as " Implant", but fall under class of transdermal delivery system these to

have been excluded from the current discussion even though they represent an exciting promising mode of drug delivery for the future.(8)

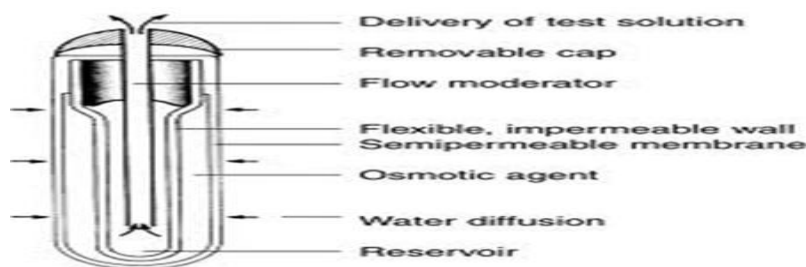


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ADVANTAGE OF IMPLANTATION DRUG DELIVERY SYSTEM:

- 1) Improved efficiency.
- 2) Very effective.
- 3) Small dose is sufficient to elicit the action. for e.g progesterone 2-8mg.
- 4) Provide linear delivery for long periods of time, from a few weeks to many months.
- 5) Plasma drug levels are continuously maintained in a therapeutically desirable range.
- 6) Patient compliance may be improved.
- 7) On spot delivery.
- 8) CONVENIENCE - Effective concentration of drug in the blood can be maintained for long period of time by techniques such as continuous intravenous infusion or repeated injections.
- 9) IMPROVED DRUG DELIVERY - The drug is distributed locally or in systematic circulation with least interference by metabolic or biological barriers.
- 10) FLEXIBILITY - In the choice of material, method of MFG degree of drug loading, drug release rate etc. considerable flexibility is possible.

DISADVANTAGE OF IMPLANTABLE DRUG DELIVERY SYSTEM:

- 1) INVASIVE - To initiate therapy either a minor or a major surgical procedure is required to initiate therapy. appropriate surgical personnel is required for this, and may be time consuming traumatic. This causes some scar formation at the site of implantation and surgery related complications in a very small number of patients. Uncomfortable feeling for the patient wearing the device
- 2) DANGER OF DEVICE FAILURE - There is no associated danger with these treatments that the device may for some reasons fail to work. These again required surgical involvement to correct.

3) **TERMINATION** - Osmotic pumps and non biodegradable polymeric implants also are surgically are recovered at the end of therapy.

4) **LIMITED TO POTENT DRUGS** - In order to minimize patients" discomfort the size of an implant is usually kept small therefore most implant have a limited loading capacity so that frequently only somewhat potent medicines such as hormones may be appropriate delivery by implantable device.

5) **BIOCOMPATIBILITY ISSUES** - Concerns over body reaction to a foreign substance often increase the issues of biocompatibility and safety of an implant.

6) **POSSIBILTY OF ADVERSE REACTION** - A high concentration of the drug delivery by an implantable device at the implantation site may produce adverse reaction.

7) **COMMERSIAL** - An enormous amount of RandD investment, effort and time is required in the development and an IDDS if a new material is purpose to formulated an implant its compatibility.

LIMITATION OF THE IMPLANTABL R DRUG DELIVERY SYSTEM :-

- * Possible toxicity
- * Need for microsurgery to implant the system
- * Possible pain
- * Difficulty in shutting of release if necessary

DRUG RELEASE DEPENDS UPON :-

- * Diffusion of drug through the polymer.
- * Non biodegradable polymers use to prepared dosage form, for e.g. polymethylsiloxane.
- * Dissolution of the drug, and usage of biodegradable polymer, for e.g. polylactic acid and polyglycolic acid.

IDEAL PROPERTIES OF IMPLANTABLE DRUG DELIVERY SYSTEM :-

- * Environmental stable.
- * Biocompatible.
- * Sterile.
- * Biostable.
- * Improve patient compliance by reducing the frequency of drug administration over the entire period of treatment.

*Release the drug in rate controlled manner that leads to enhanced effectiveness and reduction in side effects

* Readily retrievable by medical personnel to terminate medication.

*Easy to manufacture and relatively inexpensive.

WHY IMPLANTABLE DEVICE FOR DRUG DELIVERY?

Implantable drug delivery device offers several advantages over conventional oral or parenteral forms. First, implantable device allow site specific drug administration where the drug is most needed. Example include implants used in the treatment of brain tumors (Gliadel wafer) or prostate cancer (Lupron depot). This may also allow for significance lower doses of drug which can minimize potential side effects. second implantable device allow for sustained release of therapeutic agent as highlighted in the accompanying the last and perhaps most important advantage is patient compliance as the treatment regimen associated with an implantable device is generally less burdensome than pills or injection.

OPPORTUNITIES IN WOMENS HEALTH:

In addition to subcutaneous implant novel drug delivery forms such as intravenous uterine device and intra-vaginal rings and are finding increasing application in the area of women's health. for more than two decades after serious safety issues were encountered with the dalkon shield no IUDS were marketed in the US in 2000 the FDA approved levonogestrel eluting IUD (minena) providing contraceptive for up to 5 years of use. Later, use of the device was expanded to include an indication for severe menstrual bleeding and a smaller device (skylar) has been approved for children IUDs are commercially available for contraception (Nuvaring) hormone replacement therapy (Estering) to improve the rate of in vitro fertilization in development.

EVALUATION PARAMETERS FOR IMPLANTS:

1) Uniformity of weight - These test performed to maintain uniformity of weight of each implant. this is done by weighing 20 implant at random and average weight is calculated. not more than two of the individual weights deviate from the average weight by more than % and none deviate by more the %. Mean and standard deviation were determined and reported.

2) Diameter of implants - The length and diameter of implants from every batch were measured with the help of vernier calipers. There samples were taken for the study from each batch and mean value was reported.

3) Procedure of drug content uniformity test - The content of implant's from every batch was estimate. the implants were cut into small pieces and were into 50 ml volumetric flask 45 ml of glacial acid was added shaken thoroughly to dissolve the drug and the volume was made up to 50 ml with glacial acetic acid these solution was suitably diluted with acetic acid assayed for temozolomide contain by measuring the absorbance at 330nm temozolomide contain were calculated using the standard calibration curve.

4) % Swelling index - To study swelling index, the implant formulations were immersed into swelling solution phosphate buffer PH 7 the implants were place in swelling solution and weight of implant was measured after 1 hour, and excess of solution was removed gently by papping the surface with a dry piece of filter paper.

5) Drug polymer interaction study - The IR spectra of temozolomide and its formulation were obtained by KBr pellet method using perkin elmer fourier transform infrared (FTIR) series model 1615 spectrometer. The sub dermal implants of temozolomide prepared with carbopol were tested for compatibility of the drug with the excipients by IR study.

6) Stability study - The purpose of stability testing the international conference on harmonization (ICH) 2004 is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such temperature humidity and light, enabling recommended storage condition retest periods and shelf lives. evaluated for their physical appearance and drug content at specified intervals of time.

7) In vitro dissolution studies - Dissolution test was carried out using USP XXIV rotating paddle method 0.1N HCL Was used as dissolution medium, and the stirring rate was maintained at 50 rpm and temperature. each dissolution study was performed for three times and the mean values were taken

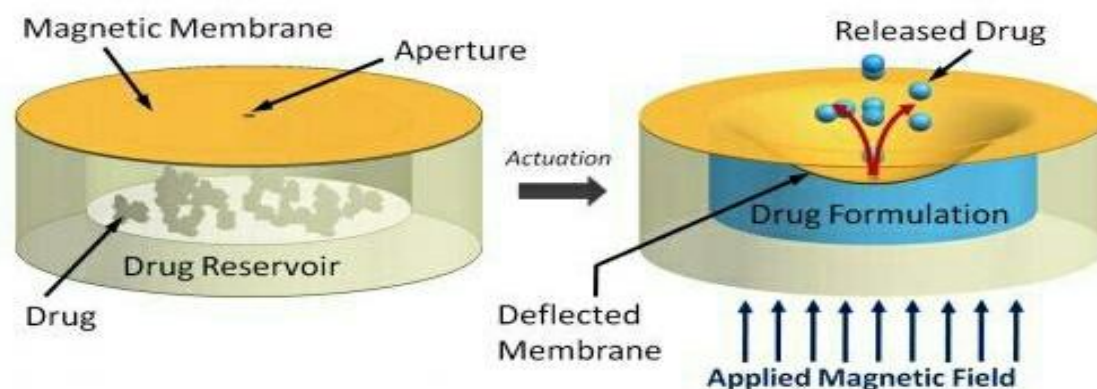


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CHRONIC DISEASE:

GLAUCOMA:

Glaucoma is the leading causes of permanent blindness and visual impairment worldwide. It is widely recognized as a multi factorial and neurodegenerative disorder characterized by the progressive degeneration of retinal ganglion cells (RGCs) that form the optic nerve. Elevation of intra ocular pressure (IOP) is major risk factor for onset and progression of glaucoma especially in primary open- angle glaucoma. However treatment of IOP exclusively will not be efficient for many reasons. (1) There are many cases of glaucoma that do not have associated IOP elevation (low tension glaucoma) (2) there are cases of elevated IOP that did not result in glaucoma and (3) there are cases where progression of glaucoma cannot be controlled by management of IOP

It is estimated that by the year 2020 about 80 million people worldwide will be affected and close to 11 million will be bilaterally blind because of the disease. It is expected that there will be a 50% increase in the no. of people that will be afflicted with glaucoma within the next 15 years based on projected expansion of the aging population. Most effective strategies of glaucoma management will require intraocular delivery system for neuro-protective agent to halt/ reverse the associated neuro-degeneration while addressing associated factors (such as elevated intraocular pressure (IOP))

OVERVIEW OF IMPLANTABLE DRUG DELIVERY SYSTEM INCLUDE THE FOLLOWING

- 1) Sustained delivery of drug to the desired segment of eye.
- 2) Ability to tailor drug delivery to the natural progression of the diseases.
- 3) Achieve high ocular drug bioavailability
- 4) Improve local drug activity while allaying concerns of systemic side effect or complication at the site of administration.
- 5) Drug administration should be noninvasive or minimally invasive without interfering with vision.
- 6) Drug delivery platform should be safe and nontoxic while ensuring patient acceptance.

CANCER:

Silicone rod implant's analogues to those used for delivery of levonorgestrel have been evaluated for delivery of ethinylestradiol or testosterone propionate in persons with prostate cancer. Lupron depot produced by Takeda chemical industries is an implantation system

providing one month depot release of leuprolide acetate, a synthetic analogue of the gonadotropin-releasing hormone (GhRH). The implant containing biodegradable microsphere made from polylactic glycolic copolymer at 1:1 composition having 10% leuprolide acetate for the management of prostate cancer. Zoladx produced by ICI pharma provide one month depot release of goserelin acetate from a biodegradable implantable rod for the management of prostate cancer.

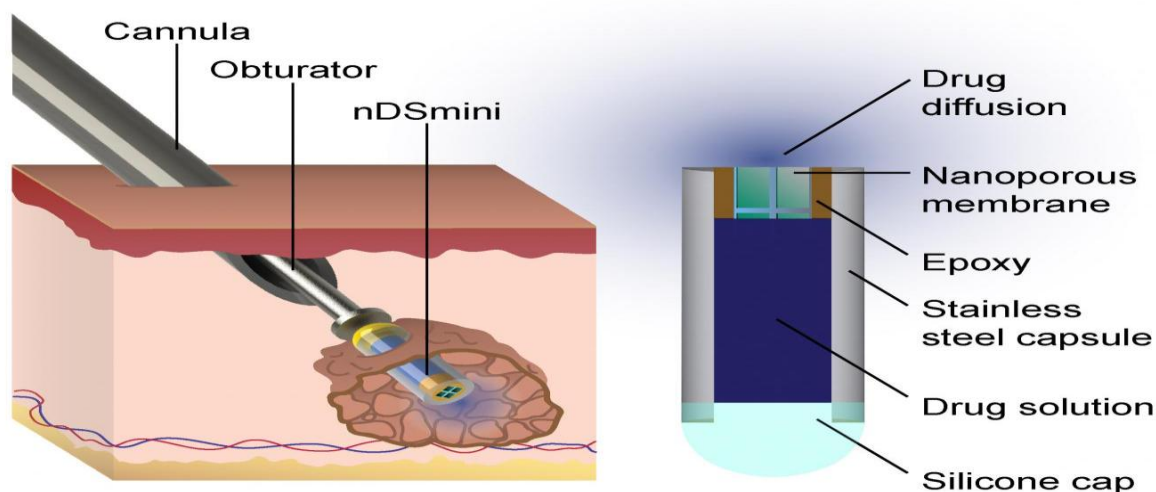


Fig no: 1.4

Non-degradable and biodegradable implant systems:

Non degradable systems:

There is several type of non-degradable implantable drug delivery systems available on the marketplace today but the no degradable matrix systems and reservoir system are the two most common forms. In the polymeric matrix systems the drug is dispersed homogeneously inside the matrix material slow diffusion of the drug through the polymeric matrix material provides sustained release of the drug from the delivery system.

The reservoir type system on the other hand consists of a compact drug core surrounded by permeable non-degradable membrane whose thickness and permeability properties can control the diffusion of the drug into the body. The release kinetics of drug from this system suggest that if the concentration of the drug within the reservoir is in constant equilibrium with the inner surface of the enclosed membrane the driving force for diffusion release of the agent is constant and zero-order release kinetics of the drug from the delivery system is obtained. This type of system however has several disadvantages. The outer membrane most of these system is non-degradable. Therefore, after drug has been released minor surgery is necessary for the removal of the delivery system from the body. There is also a possibility

that membrane rupture will potentially lead to drug dumping during therapy depending on the type of drug involved in the reservoir drug dumping may result in untoward toxic side effects from drug plasma concentration that exceed maximum safety levels. The possibility of drug dumping has made the reservoir system a less popular method of drug delivery.

Biodegradable systems:

Biodegradable systems have gained much popularity over non-degradable delivery system. The major advantages of bio-degradable system include the fact that the inert polymer used for the fabrication of the delivery system are eventually absorbed or excreted by the body. This alleviates the need for surgical removal of the implant after the conclusion of therapy thereby increasing patient acceptance and compliance.

However developing biodegradable system is a more complicated task than formulating non-degradable systems. When fabricating new biodegradable systems many variables must be taken into consideration for instance the degradation kinetics of the polymer in vivo must remain at a constant rate to maintain sustained release of the drug many factors can affect the rate of degradation of the polymer in the body. Alterations in body PH or temperature can cause a transient increase or decrease in the degradation rate of the system.

APPROCHES:

IMPLANTABLE PUMP SYSTEM:

Many different drugs require external control of delivery rate and volume. Such control cannot be obtained when using bio-degradable or non-biodegradable delivery systems with the exception of the magnetic-type delivery systems. Pump systems have been used to provide the control needed in these situations. Recently, due to the availability of advanced micro technology, it has been possible to create pump systems small enough to implant, subcutaneously, for drug delivery. this allows the patient to maintain the control of drug release without the need for an external pump system. In recent advanced, insulin implantable pump systems have been invented and used for the control of type-1 diabetes as shown in fig.3

Pump systems differ from other implantable systems due to their mechanism of drug delivery. pump systems release drug through a pressure difference generated gradient that result in the bulk flow of a drug at controllable rates. to date, five different types of implantable pump systems have been tested including infusion pump, peristaltic pumps, osmotic pumps, positive displacement pumps, and controlled release micro pumps.

INFUSION PUMP:

Infusion pumps are implantable mechanical systems that utilize a fluorocarbon propellant to administer the drug. *in vivo* such pumps were initially developed for the administration of insulin to diabetic patient. Infusaid was one of the first commercially available pumps for this use. Normally insulin dependent diabetic require injections once or twice daily. The force of injection recompresses the fluorocarbon propellant thereby recharging the system. In addition to insulin therapy the use of this pump system in the delivery of anticoagulant and chemotherapeutic agent has also been investigated.

PERISTALTIC PUMP:

Peristaltic pump consist of rotary solenoid driven systems that run via an external power source which is usually a battery. Peristaltic systems like the infusion p[ump system are filled through a silicon rubber septum and can be used for several year depending on the life span. The advantage of this type of system is that the rate of drug administration can be controlled by an external remote control system.

OSMOTIC PUMPS:

Osmotic pumps have proven to be the most popular type of implantable drug delivery system. The osmotic pump also known or oros or the gastrointestinal therapeutic system, was first described by Theeuwes and Yum and released for use by Alza Corporation. These pumps consist of a drug reservoir surrounded by a semi permeable membrane. The surrounded membrane allows a steady influx of water and biological fluid into the reservoir through the process of osmosis. The hydrostatic pressure built from this influx cause a steady release of the drug from an opening in the membrane called the drug portal. The rate of drug release is constant or zero-order until the drug within the drug within the reservoir is completely depleted. Changing the rate of drug administration of these systems can only occur by changing the structure of the semi permeable membrane that require removal of the system.

POSITIVE DISPLACEMENT PUMPS:

Positive displacements pumps have been developed tom provide continual insulin delivery in diabetic patients. Most of these systems utilized piezoelectric disk bender affixed to flexible tubing. such pumps are made by first exposing the disks to certain voltages so that they form spherical surface. The bellow type system is then connected to a drug reservoir via a three way solenoid driven value in the pump open or close depending on the direction of pulse.

IMPLANTABLE RODS:

Implantable rods are prepared with the help of different type of bio-degradable and non bio-degradable polymers the implantable rod release the drug in a control manner.

CONCLUSION:

A research work and novel technique is currently being conducted in the area of implantable drug delivery system. However, much work is still needed in the areas of biodegradable and biocompatible materials the kinetic of drug release, and further development of current system before many of these formulations can be use. In the future researcher remain hopeful that many these system can be developed with ideal zero ordered release kinetic profiles in vivo, over long period of time, allowing for extended use in chronically ill patient.

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