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IMPLANTABLE DRUG DELIVERY SYSTEMS: AN RECENT REVIEW

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ABSTRACT

Implantable drug delivery is a new technology which offers in the development of new drug delivery by many pharmaceuticals. Implant drug delivery technologies deliver the drug in control manner .Many products used delivery technologies are being used in various therapeutic applications, such as dental, ophthalmic, and oncological diseases. With this foundation, the present review aims to focus on recent technologies in implantable drug delivery."

Keywords: Recent Technologies, Monolithic, Implantable Drug Delivery, Control Drug, Fabrication.

I. INTRODUCTION

Drug delivery through implant systems, known as Implant Drug Delivery Systems (IDDSs), is highly appealing for various classes of medications, especially those that cannot be administered orally, are unevenly absorbed through the digestive system, or benefit from precise dosing. This includes drugs like steroids, chemotherapy agents, antibiotics, pain relievers, contraceptives, and biologics such as insulin or heparin. Implants can serve for either systemic or localized therapeutic purposes. For systemic effects, implants are typically introduced subcutaneously, intramuscularly, or intravenously, where the embedded drug is gradually released into the bloodstream. Implants designed for local effects are positioned in specific body sites, allowing the drug to act locally with minimal absorption into the systemic circulation. These implants are engineered to release the drug in a controlled manner, enabling adjustment of release rates over extended durations, ranging from days to years. Morphologically, implants are usually cylindrical, with monolithic devices ranging from millimeters to centimeters in scale. Implantation is typically carried out using specialized tools like needles or through surgical procedures in subcutaneous or intramuscular tissue. These tissues are preferred for drug depot implants due to their high fat content, which facilitates slow drug absorption, minimal nerve supply, good blood flow, and a reduced risk of local inflammation. In addition to subcutaneous implantation, various other body regions, such as intra-vaginal, intravascular, intraocular, intrathecal, intracranial, and peritoneal areas, are explored for targeted localized drug delivery. One of the most common clinical applications is for drug-eluting stents (DES) targeting cardiac or carotid arteries, facilitating therapy delivery to intravascular locations.[1]

Types of implant drug delivery systems:

Classification**:**

1 Rate programmed Drug Delivery System:

➡ Membrane permeation

➡ Matrix diffusion

➡ Membrane matrix hybrid type

➡ Microreservior partition- controlled

2 Activation Modulated Drug Delivery:

1. Physical activation:

➡ Osmotic pressure

➡ Vapour pressure Phonophoresis

➡ Hydration

➡ Magnetically activated

2. Chemical activation:

➡ Hydrolysis

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3 Feedback Regulated Process:

➡ Bio-erosion

➡ Bio-resonsive [2,3,4]

Advantages of Implantable Drug Delivery System:

1. Convenience: Implantation treatment permits patients to get medication outside the hospital setting with marginal medical observation.

2. Prolonged Drug Concentration: Effective concentration of the drug in the blood can be maintained for a longer period of time.

3. Comparison to Traditional Methods: Traditional methods, such as continuous intravenous infusions or repeated injections, require patients to regularly visit the hospital throughout administration for uninterrupted medical monitoring. A short-acting medicine can worsen the condition, as the quantity of injections or the infusion rate needs to be increased to maintain a therapeutically effective level of the drug." It's true that certain treatments may have a lower occurrence of infection-related issues when compared to indwelling catheter-based infusion systems. This can be attributed to the reduced risk of introducing pathogens into the body through alternative treatment methods.

4. Potential for Controlled Release: Implants offer zero-order controlled release kinetics, which helps to avoid peaks (toxicity) and troughs (ineffectiveness) of conventional therapy. This also reduces dosing frequency and increases patient compliance.

5. Potential for Intermittent Release: Extremely programmable pumps enable intermittent release of drugs in response to factors like cardiac rhythm, metabolic needs, and pulsatile release of many peptides and proteins.

6. Improved Drug Delivery: Implants provide benefits by distributing the drug locally or in systemic circulation while bypassing or minimally interfering with metabolic or biological barriers. This is particularly advantageous for drugs absorbed in the gastrointestinal tract and liver before systemic distribution.

7. Compliance: Patient compliance can be significantly improved due to the reduction or complete elimination of patient-involved dosing. Although certain implants may require periodic refilling, the patient has very little involvement in delivering the medication.

8. Flexibility: Implants offer various types of flexibilities, such as materials, methods of manufacture, degree of drug loading, and drug release rate. They permit controlled delivery of both hydrophilic and lipophilic drugs.

9. Let me know if you would like any further adjustments or if you have more sentences to reorganize.

Disadvantages of Implantable Drug Delivery System:

1. Invasiveness: Implantation often requires major surgery, leading to scarring and discomfort. Skilled personnel are needed for the procedure.

2. Termination: Non-biodegradable implants necessitate surgical removal after treatment, adding another medical procedure.

3. Device Failure: If the implant malfunctions, it must be surgically removed, posing potential risks.

4. Limited Drug Capacity: Implants are typically small to reduce patient discomfort, limiting the amount of medication that can be delivered, making them suitable mainly for potent drugs.

5. "Dose dumping occurs at the site of implant, leading to severe adverse reactions. This indicates the possibility of drug reactions[5-8].

Implantable devices :

There are various devices are used to deliver drug in the body part.

List of implantable devices :

(A)Field of Controlled Drug Delivery:

- Transdermal patches
- Polymer implants
- Bioadhesives
- Microencapsulation

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- Some important passive devices:

a. Microchip drug reservoirs
b. Immuno-isolating capsules
c. Diffusion chambers
d. Diffusion controlled implanted tubes

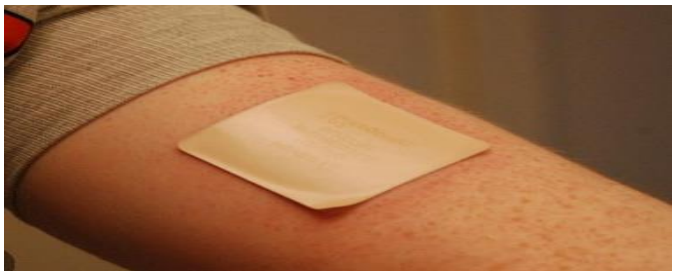
(B)Implantable Pump Systems:

- Medtronic synchromed
- Debiotech

(A)Field of Controlled Drug Delivery:

The field of controlled drug delivery today employs mechanisms such as transdermal patches, polymer implants, bioadhesive systems, and microencapsulation Implantable controlled drug delivery methods are also useful to deliver medication to those parts of the body which are immunologically isolated and regular modes of drug delivery cannot reach them, for example, the cornea."[9-11]

1. Transdermal Patches:



The field of controlled drug delivery today employs mechanisms such as transdermal patches, polymer implants, bioadhesive systems, and microencapsulation. Implantable controlled drug delivery methods are also useful to deliver medication to those parts of the body which are immunologically isolated and regular modes of drug delivery cannot reach them, for example, the cornea.[12]

2. Polymer Implants:

Polymer implants, such as those made from Polyglycolic acid (PGA), Polylactic acid (PLA), Polyurethane, and their combinations, are designed to deliver drug molecules gradually by degrading in contact with body fluids. The rate of degradation and drug release can be controlled by adjusting the properties of these polymers. These biodegradable polymers are widely used in various medical applications for controlled drug delivery

3. Bioadhesives:

The most common substances used in this case are polymer hydrogels. Hydrogels are water-swollen polymer networks. The polymer chains may be held together by either physical forces or covalent crosslinks. By design of the hydrogel constituents, they can be made responsive to their chemical or physical environment. Bioadhesives are substances that form bonds with biological surfaces. The principle of operation is similar to polymer implants in that they too are loaded with drugs and release drugs at a specific rate when in contact with body fluids. At a temperature of 35-40 ºC, it collapses into a denser, more compact structure due to a switch in the balance of solution and hydrophobic forces as the temperature is raised [13].

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4. Microencapsulation:

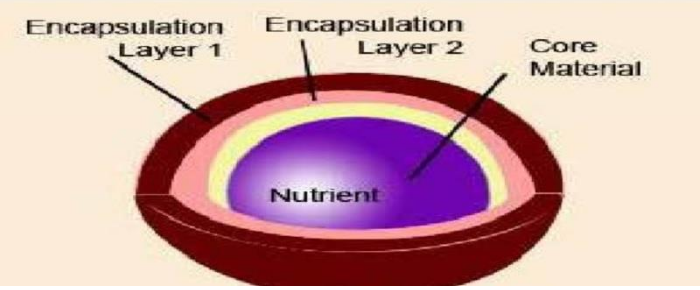
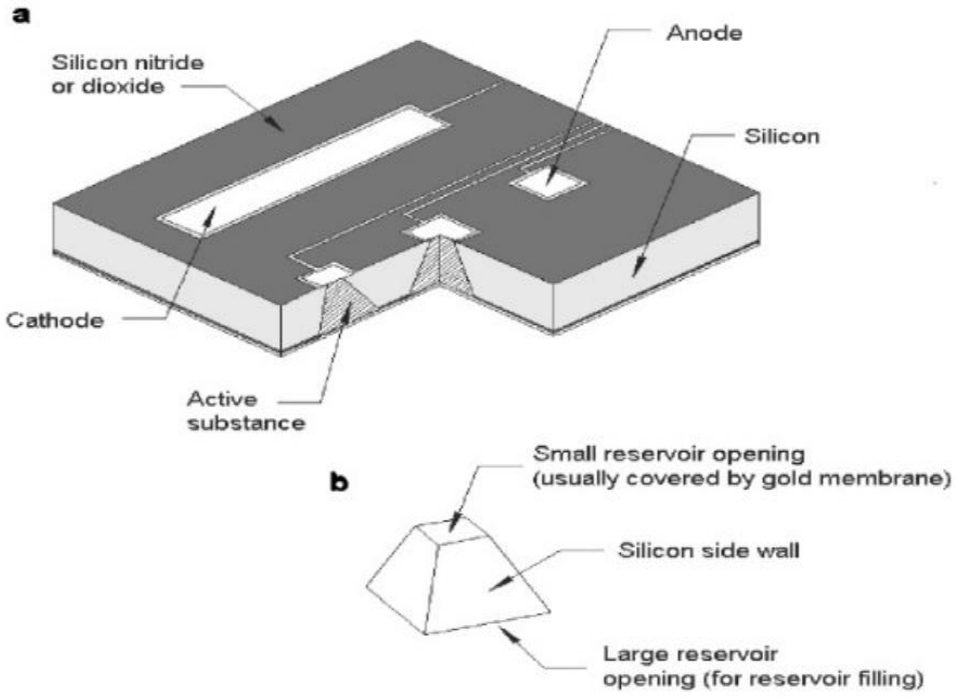


Fig: (Microencapsulation)

"Microencapsulation is achieved through various methods, including the use of polymer microspheres, liposomes, nanoparticles, and more. It involves covering the drug molecule with a material that extends the time before the drug is resorbed. This approach ensures that the drug remains in a viable state and is released when it reaches its intended destination."

[12]While these devices are effective at delivering the drug gradually in precise, small amounts, they are 'passive devices' and do not have the capability to provide the drug in a non-linear fashion or on demand. They cannot be programmed to release the drug when needed and stop when it is not required [10, 11]."

5. Some Important Passive Devices:



a. Microchip Drug Reservoirs:

Developed in the lab of Dr. Robert Langer at MIT, this is one of the very first truly MicroElectro Mechanical Systems (MEMS) based drug delivery systems (see Figure 4.1). The design features multiple sealed compartments, which can be opened on demand to deliver a dose of a drug [11]."The fabrication of these microchips began with the deposition of 0.12 mm of low-stress silicon nitride on both sides of prime grade (100) silicon wafers using a vertical tube reactor. An etch mask for potassium hydroxide solution at 85.8ºC was provided by the silicon nitride layer on one side of the wafer, which was patterned using photolithography and electron cyclotron resonance (ECR) enhanced reactive ion etching (RIE). This resulted in a square device (17mm x 3mm x 17 mm) containing 34,480 square reservoirs. These square pyramidal reservoirs were anisotropically etched into the silicon along the (111) crystal planes until reaching the silicon nitride on the opposite side of the wafer (Figure 4.1 b)

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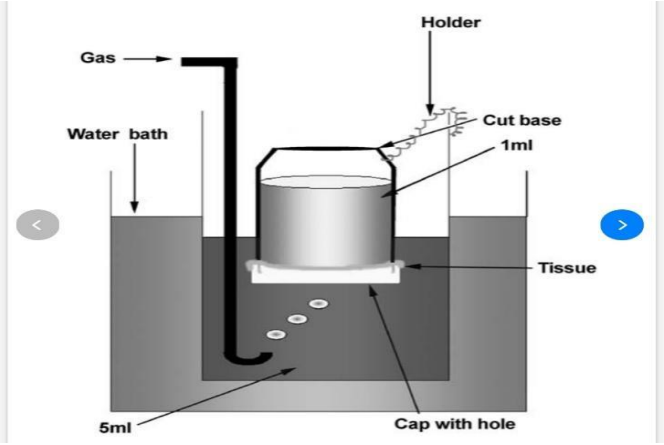
b. Immuno-isolating Capsules:

Microfabrication techniques have been applied to create a biocapsule for effective immunoisolation of transplanted islet cells for the treatment of diabetes. These devices are not drug delivery systems in the conventional sense. They contain pancreatic islet cells which make insulin and deliver it through the nanoporous membrane of the device, rather than storing it in the device. They deliver insulin in the body."[14]

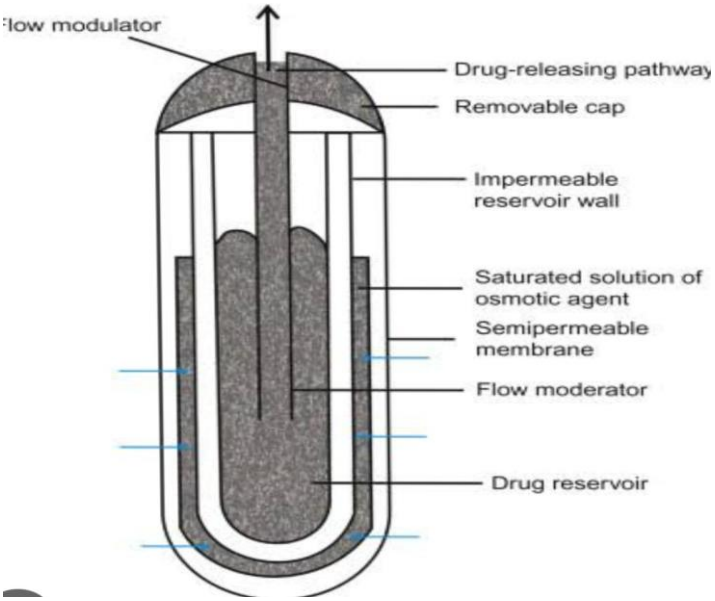
The fabrication of nanochannels in the membrane structure consists of two steps. First, surface micromachining nanochannels in a thin film on the top of a silicon wafer. These nanopore membranes are bonded to a capsule that houses the pancreatic islet cells. Because the difference in the size of insulin, which must be able to pass freely through the pores and the size of the IgG immunoglobulins, which must be excluded, is only a matter of a few nanometers, the highly uniform pore distribution provided by micromachine membranes is essential for effective immunoisolation and therapeutic effect. Second, releasing the membrane by etching away the bulk of the silicon wafer underneath the membrane. At the same time, they prevent the passage of cytotoxic cells, macrophages, and complement. The membranes are designed to allow the permeability of glucose, insulin, and other metabolically active products."

c. Diffusion Chambers:



They hold a cargo of drugs and are sealed with a semipermeable membrane. The membrane surface area is large compared to the reservoir resulting in the increased delivery rates. These are used for delivering fairly large amounts of drugs and, in some cases, more than one drug. These reservoirs are generally not used for long-term delivery[28]. A diffusion chamber from Debiotech Inc."[15

d. Diffusion Controlled Implanted Tubes



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They use a narrow aperture to provide a slow delivery rate of drugs. A good example is the five-year-duration birth control implants based on elastomeric tubes[33]. They are used for long-term release of highly potent drugs, with the release times in the order of years."[33]The DurosTM osmotic pump from ALZA Corporation is a similar example. This nonbiodegradable, osmotically driven system[2] is intended to enable delivery of small drugs, peptides, proteins, DNA, and other bioactive macromolecules for systemic or tissue-specific therapy. The DUROS® implant is a miniature cylinder made from a titanium alloy, which protects and stabilizes the drug inside, using ALZA's proprietary formulation technology. Water enters into one end of the cylinder through a semi-permeable membrane; the drug is delivered from a port at the other end of the cylinder at a controlled rate suitable for the specific therapeutic agent.

(B) Implantable Pump Systems:

The development and commercialization of the unit was a joint effort between industry and academia, in this case the University of Minnesota and the Infusaid Company. It used a bellows-type pump activated by partially liquefied Freon. The Freon was reliquified with each transcutaneous refill of the implantable device, and the administration of the drug was constant. There were no electronics or batteries in the device.But the later devices by the same company and Medtronic came with significant advancements. These more sophisticated units include a refillable reservoir, a mechanical pumping/valving mechanism, advanced electronics that control the drug administration, and which can be programmed telemetrically from outside the body, and a primary lithium battery.The first such device to see extensive clinical use was reported in the early 1970s. The primary characteristic that distinguishes a pump from other controlled-release systems is that the primary driving force for delivery by a pump is not the concentration difference of the drug between the concentration and surrounding tissue, but rather, a pressure difference. This pressure difference can be generated by pressurizing a drug reservoir, by osmotic action, or by direct mechanical actuation."[16]

1. Medtronic Synchromed:

The most widely used Implantable drug delivery system is the Minimed Medtronic Insulin delivery pump. As the name suggests, it is used as an artificial pancreas for patients with Diabetes Mellitus. The Minimed pump (which is the maker of the pump later acquired by Medtronic) has a peristaltic minipump[17] which delivers 0.50µl per stroke. Depending upon a patient's insulin requirements, the implantable insulin pump reservoir is refilled with fresh insulin every two to three months. A needle is inserted through the skin into the pump fill port. To assure refill safety, the negative pressure in the pump will automatically draw the special U-400 insulin from the syringe into the reservoir only after the needle has been securely connected inside the fill port [18]."

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2. Debiotech:

The MIP implantable pump will perhaps be The first MEMS based implantable pump to enter the market. It is proposed that it is going to be the heart of a high performance programmable implantable drug delivery system. The MIP is a piezo-actuated silicon micropump. The working principle is a volumetric Pump with out-of-plane pumping membrane, which compresses a chamber in a reciprocating movement and which is associated to a pair of check valves in order to direct the liquid flow. The chip is a stack of four layers bonded together: two (purple) silicon Plates with micromachined pump structures and two (dark blue) glass pieces with through-holes. Added to the stack is a piezoelectric ceramic disc (green), responsible for the actuation and two titanium fluid connectors (grey), hermetically joined to the chip.[19]

II. APPLICATIONS

1. Biomedical application:

- Parenteral controlled administration of drugs via subcutaneous or intramuscular drug delivery device can gain easy access to the systemic circulation to achieve a total bioavailability of drugs as well as a continuous delivery of drugs, in contrast to transdermal, oral, etc. routes of administration.
- An implantable drug delivery system offers a significant advantage over injectable controlled release formulations

2. Human application:

- Nowadays, several biodegradable subdermal implants have been made with the help of biodegradable polymers.
- A new generation of subcutaneous contraceptive implant, “Implanon,” is recently developed, and it is also a sandwich-type implant device.
- Continuous heparinization in anticoagulation treatment with the help of an Infusaid pump is also available today.
- Infusid pumps are also applied for the intravenous controlled infusion of insulin for the continuous treatment of diabetes. A soluble insulin preparation is used as the drug reservoir in this case.

3. Veterinary application:

- For veterinary applications, several implantable drug delivery devices have been prepared from biocompatible polymers.
- Investigation of biocompatibility is necessary, including examining the formation of a fibrous capsule around the implant and assessing the potential toxicity or immunogenicity of the by-products of polymer degradation in the case of erosion-based devices. [20,21

III. FUTURE PROSPECTS

Much research is currently being conducted in the region of implantable drug delivery systems. Scientists remain expectant that many of these systems can be prepared with the best zero-order release kinetics profiles in vivo, over long times, allowing for prolonged use. In the future, improvements in new implantable systems are expected to help reduce the cost of drug treatment, increase the effectiveness of drugs, and enhance patient compliance. This is particularly important since several of these medicines are continuously developed from proteins and peptides, which are very unstable when taken orally. Despite this fact, much work is still required

in the regions of biodegradable and biocompatible substances, the kinetics of drug release, and further improvement of the present systems before many of these preparations can be used. Using new types of prolonged-release drug delivery systems will make it possible to deliver such drugs at constant rates over an extended period of time, eliminating the need for multiple dosing.[22,23]

IV. CONCLUSION

The majority of medicines are responsible for all the drug delivery systems. An implantable drug delivery system is an efficient and good drug delivery system and releases the drug over a long period. Implantable drug delivery system shows controlled or zero-order release of the drug and is also used for targeted drug delivery systems, like contraceptive implants that are used to prevent pregnancy. Such implants are placed into the uterus by small surgery, and these implants release the drugs over a period of up to 10 years. Implantable drug delivery systems have a wide range of advancements, such as zero-order release, reduced toxicity, targeted drug delivery systems, less amount of drug required, and enhanced individual compliance. Sometimes implants also lead to fewer hospitalizations, which develop novel areas in healthcare professions. In this study, it is also described how the implant releases the drug from it, and four methods of drug release are mentioned in the above study. This study will help in future studies on the implantable drug delivery system. The drug can be administered by various routes like oral drug delivery, transdermal, and implant, etc. This study will also help in the selection of a suitable polymer for implant preparation, as two types of polymers are used, that is, biodegradable and non-biodegradable polymers. Non-biodegradable polymers are most commonly used in diffusion-controlled implantable systems. This study includes the approaches in the implantable drug delivery system, formulation and preparation of implants, and also the evaluation parameters.

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