

Review on Implantable Drug Delivery System

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Abstract: *In the past, medications were commonly given orally in the form of liquids or powders. However, to address the challenges associated with oral drug administration, alternative dosage forms were developed. Over time, the need arose for drug delivery systems capable of providing a consistent release of medication directly to the site of action. This led to the creation of drug delivery technologies aimed at enhancing the therapeutic effects of drugs while making them safer, more effective, and reliable. Implantable drug delivery systems (IDDS) are one such innovation currently used in treatment. These systems offer several key benefits, including targeted and steady drug release, reduced dosage requirements, fewer side effects, and improved treatment outcomes. Thanks to advancements in sustained release formulations, medications that once required multiple daily doses can now be administered weekly or even annually. Early studies have demonstrated that these systems are more effective than traditional treatment methods. Nonetheless, a major drawback is their high-cost relative to their benefits, which limits their widespread adoption. Furthermore, many newly developed implants are still in early stages and need thorough clinical testing before they can be used routinely in healthcare settings*

Keywords: Implantable drug delivery system, stents, pumps, transdermal patches, drug delivery systems, recent technologies

I. INTRODUCTION

In 1861, Lafarge introduced a term for the sustained release of drugs. Implants, which are bitty pellets made purely of the drug without any excipients, fall under this order. These implantable drug delivery systems are entirely fitted beneath the skin in discreet, unnoticeable areas. Cases generally only notice a small bump under the skin. These systems are designed to deliver medicine and fluids directly into the bloodstream, barring the need for frequent needle injections. They are especially suitable for administering insulin, steroids, chemotherapeutic agents, antibiotics, pain relievers, total parenteral nutrition, and heparin. Since the device is fully subcutaneous and does not break the skin's face, the trouble of infection is minimal and it does not intrude with quotidian exertion^[1]. An orally administered drug must be shielded against declination in the gastrointestinal(GI) tract and should be efficiently absorbed through the stomach or intestinal stuffing. Once absorbed into the portal gyration, it must also repel breakdown by liver enzymes. To be effective, the drug's absorption and elimination rates should maintain its attention in the blood within the remedial window. The drug amount that reaches the target point must be sufficient to produce the asked remedial outgrowth without causing dangerous side goods. Controlled drug release can be achieved either through chemical modification of the drug itself or by designing specific phrasings that regulate its release. Oral controlled- release capsule forms can maintain effectiveness for over to 24 hours; still, they are limited by the GI tract's fairly long vehicle time of about 12 hours. When oral administration is not doable, parenteral routes analogous as intravenous injection are used, especially for proteins, peptides, and other drugs vulnerable to GI conditions. nonetheless, intravenous drugs generally have a short duration of action, taking frequent dosing. Injectable controlled- release phrasings are considered more commercially doable compared to other delivery styles, handed they ensure both effectiveness and safety. Topical administration, on the other hand, faces challenges due to limited drug penetration through the skin's outermost caste, the stratum corneum. In distinction, implantable drug delivery systems overcome multitudinous of the limitations associated with oral, intravenous, and topical routes. Subcutaneous implants, in particular, offer the added benefit of being retrievable if necessary^[2]. Implantable drug delivery bias is especially precious when strict adherence to a medicine schedule is essential. These systems enable precise, controlled drug release without the need for ongoing input from either the case or a healthcare provider. Being drug delivery implants generally fall into two orders unresistant and



active delivery systems. Among unresistant systems, polymer depots are the most considerably used. These are finagled to either allow drug to circumlocutory at a steady rate or to degrade at a controlled pace, thereby releasing the drug over time. In distinction, traditional programmable implantable drug delivery bias(IDDDs) devotes roughly 25 – 50 of their internal volume to a battery designed to last throughout the device’s continuance, generally 5 to 10 times. Despite this long- term battery life, these IDDDs generally bear medicine renewals every 10 weeks, which are administered via transdermal injection into a subcutaneous cache harborage^[3]. The clinical development of implantable drug delivery systems(IDDSs) gained instigation in the 1990s following the FDA blessing of Norplant ® a contraceptive implant containing levonorgestrel. This device was predicated on the" Silastic" capsule design originally proposed by Folkman and Long^[4]. presently, commercially available IDDSs are applied for the treatment of habitual conditions, gravidity control and women’s health, pain operation and internal health, and guided regeneration.

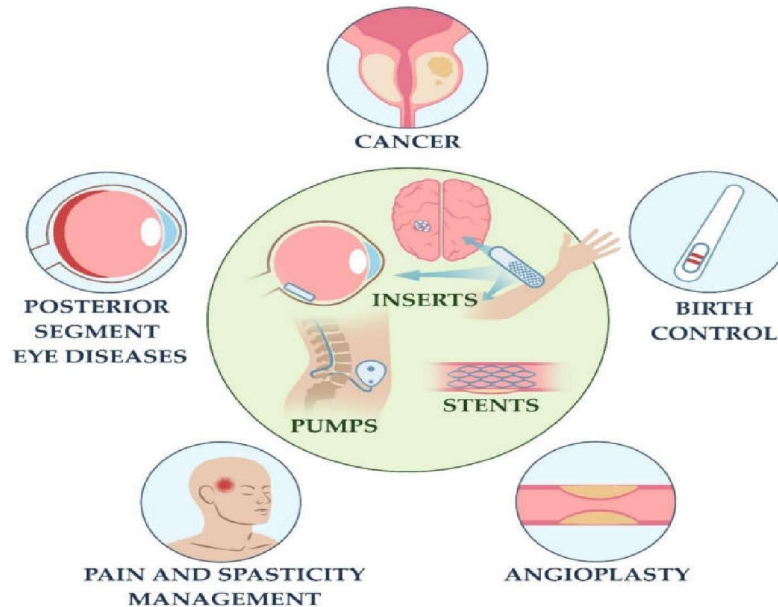


Figure 1.1Classification of IDDSs

Implants can be placed in the body through injections or small incisions, often requiring only minimal anesthesia and brief procedures, for example, with subcutaneous inserts or osmotic pumps. They can also be delivered via intravascular methods, such as stents, or through more extensive surgeries, like those needed for mechanical pumps. It’s important to recognize that the terminology surrounding implantable drug delivery systems (IDDSs) can be somewhat unclear. Terms like “implant” and “insert” are frequently used interchangeably, sometimes for marketing purposes rather than scientific accuracy. In this review, we focus on solid implants that are introduced into the body through at least a minimal surgical procedure involving tissue penetration or incision. The U.S. FDA defines an “implant” as a device placed into a surgically or naturally created cavity in the human body, intended to remain in place for an extended period typically at least 30 days, although shorter durations may also fall under this category for safety considerations^[5].

Commercially available implantable drug delivery systems (IDDSs) fall into several main categories, each with specific areas of application. The term “inserts” refers to solid implants that are surgically placed into the body. These systems typically release drugs through diffusion or osmotic gradients hence, osmotic pumps can also be categorized as inserts. Meanwhile, “pumps” usually describe reservoir-based IDDSs equipped with mechanisms that actively regulate and control drug release. Some inserts, particularly those that utilize osmotic gradients, may also be classified as pumps. Drug-eluting stents are designed to be inserted into tubular body structures, such as blood vessels, to maintain or restore patency while simultaneously preventing excessive tissue growth. Inserts are used across a broad range of medical applications, with the exception of pain and spasticity management. Stents are primarily used in angioplasty, but they



also support other procedures involving tubular structures. Pumps serve a wide variety of uses depending on the medication they deliver, with the most common applications being pain/spasticity control and cancer therapy.

The primary types of therapeutic agents delivered by implantable drug delivery systems (IDDSs) include hormones, cytostatic drugs, anticoagulants, antipsychotics, and medications for metabolic disorders. Additionally, several new areas of clinical application for IDDSs such as the treatment of mental health conditions are emerging and have reached the later phases of clinical trials.

Although there is no universally accepted classification system for implantable drug delivery systems (IDDSs), several categories have been proposed. These include biodegradable versus non-biodegradable devices, passive implants (such as inserts and stents) versus dynamic ones (like pumps), electromechanical and reservoir-based systems, as well as devices based on polymers or hydrogels. IDDSs can also be categorized by their implantation site, such as ocular, subcutaneous, or intracranial. This classification encompasses not only clinically approved systems but also those in preclinical development or undergoing clinical trials. The specific type of IDDS determines how the drug is released—whether primarily through passive diffusion, aided by osmotic gradients, or actively driven by external stimuli such as mechanical, thermal, or magnetic forces. The wide-ranging variety of IDDSs in terms of materials, design, and drug release mechanisms is thoroughly discussed in other comprehensive reviews^[4,6,7,8,9,10,11,12].

2. Ideal properties of implantable devices:

- The implant should be cost-effective.
- It should be simple to manufacture. It must allow for easy sterilization and be designed so medical professionals can remove it effortlessly if treatment needs to be stopped.
- The device should provide controlled drug release to minimize side effects and enhance therapeutic effectiveness.
- It should be enclosed in a suitable encapsulation material and must be safe, non-toxic, stable, effective, and mechanically robust.
- Additionally, the material used should be biocompatible and not cause adverse reactions when in contact with body tissues^[13,14].

3. Advantages of IDDSs:

- Reduced side effects
- Enhanced patient compliance
- Increased drug bioavailability
- Implantable drug delivery systems enable targeted drug administration^[15]
- Promote healing and support bone regeneration^[16]
- Bypass first-pass metabolism
- Designed to withstand repeated sterilization without degrading^[17]
- Miniaturization of implantable devices improves usability and reduces overall weight^[18].

4. Disadvantages of IDDSs:

- There is a possibility of infection developing where the implant is placed.
- The treatment cannot be easily stopped once started.
- Surgical intervention is required for larger implants, which can be a painful process.
- Some medications may interact negatively with implanted devices^[19].

5. Mechanism of implantable drug delivery systems:

Implantable medicine delivery systems (IDDS) use several mechanisms for medicine release, including:



5.1 Osmosis:

A semipermeable membrane encases the medicine force, permitting water to enter while precluding the medicine from escaping. As water accumulates, it builds pressure that pushes the medicine out through a small opening, enabling a controlled and nonstop release.

5.2 Diffusion:

prolixity medicine motes move from areas of advanced attention to lower attention, driven by an attention grade. This natural movement helps regulate medicine release.

5.3 Swelling:

lump Certain polymers swell upon absorbing water, altering their molecular mobility and lowering the glass transition temperature. This change helps manage how the medicine is released from the device.

5.4 Protein distribution:

In some implants, the medicine is bedded in a polymer matrix. The release process generally occurs in three stages an original burst, a prolixity- controlled phase, and a final corrosion- controlled phase. also, some IDDSs can respond to external instigations similar as light, sound, electrical signals, or glamorous fields^[20,21].

6. Implantable Drug Delivery Devices:

6.1 Field of Controlled Drug Delivery

The field of controlled drug delivery focuses on targeted methods to administer medication, particularly to areas of the body that are immunologically protected and inaccessible through conventional drug delivery techniques, such as the cornea. Current technologies in this field include transdermal patches, polymer-based implants, bioadhesive delivery systems, and microencapsulation approaches^[22-24].

6.2 Transdermal Patches

Transdermal patches typically utilize hollow microneedles made from biocompatible polymers to administer drugs beneath the skin. This method of drug delivery offers several benefits over traditional systems: it avoids drug degradation in the gastrointestinal tract, provides a painless application, and ensures a steady release of medication without relying on patient compliance^[25]. A well-known example of this technology is the nicotine patch.

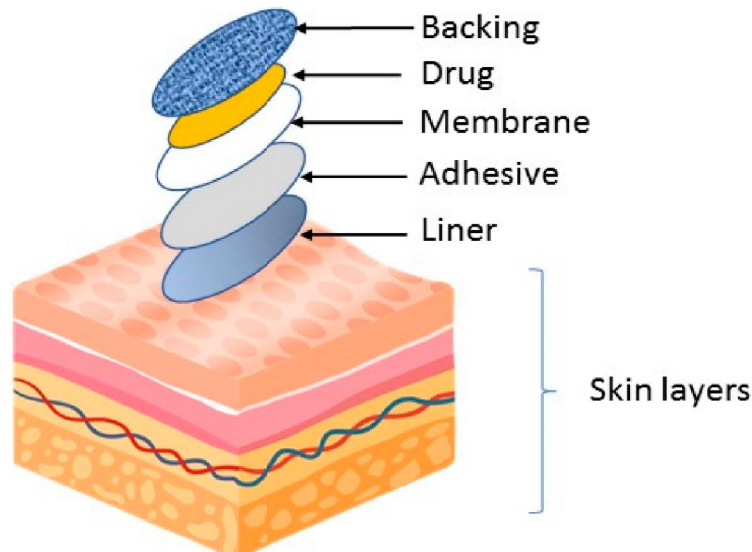


Figure 6.1 Transdermal Patches

6.3 Polymer Implants

Polymer implants are made from biodegradable polymers that contain drug molecules. When these implants come into contact with body fluids, the polymers gradually break down, releasing the drug in the process. By altering the



properties of the polymers, the rate at which they degrade and consequently, the rate of drug release can be controlled. Commonly used polymers for such applications include Polyglycolic Acid (PGA), Polylactic Acid (PLA), Polyurethane, and various combinations of these materials in different ratios.

6.4 Bioadhesives

Bioadhesives are materials that adhere to biological surfaces, with polymer hydrogels being the most commonly used type. These hydrogels function similarly to polymer implants in that they can be loaded with drugs and are capable of releasing them at a controlled rate upon contact with bodily fluids. Structurally, hydrogels are networks of polymers swollen with water, where the polymer chains are interconnected either through physical interactions or covalent bonds. By carefully selecting their components, hydrogels can be engineered to respond to specific chemical or physical conditions. For instance, at temperatures between 35 and 40 °C, they undergo a phase transition, contracting into a denser and more compact form as a result of changes in the balance between hydrophobic interactions and solubility forces^[26].

6.5 Microencapsulation

Microencapsulation is a technique used to coat drug molecules with a protective material, allowing the drug to remain stable and be released gradually upon reaching its target site. This approach helps extend the drug's activity by delaying its absorption. Various methods are employed for microencapsulation, including the use of polymer microspheres, liposomes, and nanoparticles^[25]. These systems are considered 'passive devices' as they release the drug slowly and in precise, small amounts over time. However, they lack the ability to release the drug in a non-linear or 'on-demand' manner. They cannot be programmed to start or stop drug delivery based on specific needs^[23].

6.6 Some Important Passive Devices

6.6.1 Microchip Drug Reservoirs

This bias began from Dr. Robert Langer's lab at MIT and represent one of the foremost true MicroElectroMechanical Systems (MEMS) grounded medicine delivery platforms (Figure 4.1).

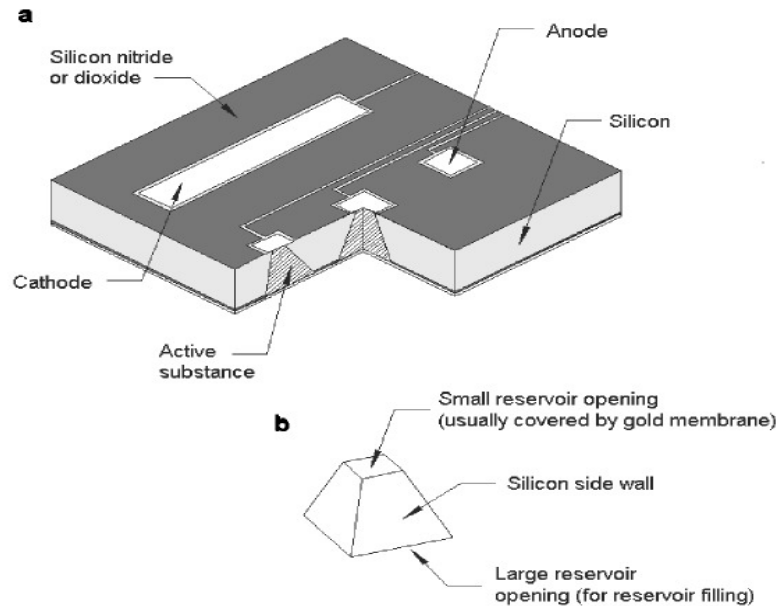


Figure 6.1 Microchip Drug Reservoir



The system features multiple collectively sealed chambers that can be widely opened to release precise medicine boluses on demand^[24]. The microchip fabrication process began with the deposit of a 0.12 mm low- stress silicon nitride subcaste on both sides of high- grade(100) silicon wafers using a perpendicular tube reactor. Photolithography and electron cyclotron resonance(ECR) enhanced reactive ion drawing(RIE) were also used to paint the silicon nitride subcaste on one side, forming square bias measuring 17 mm × 3 mm × 17 mm and containing 34,480 square budgets. This patterned nitride subcaste acted as an outline mask during anisotropic drawing with potassium hydroxide at 85.8 °C. The result etched square pyramidal budgets into the silicon along the(11) demitasse aeroplanes until it reached the silicon nitride subcaste on the wafer's contrary side(illustrated in Figure 4.1 b).

6.6.2 Immuno-isolating Capsules

These devices do not function as traditional drug delivery systems. Instead of storing and dispensing insulin directly, they house pancreatic islet cells that naturally produce insulin. The insulin is then released through a nanoporous membrane. Using microfabrication techniques, researchers have developed a biocapsule that effectively isolates transplanted islet cells from the immune system, offering a potential treatment for diabetes^[27]. The creation of nanochannels in the membrane involves two main steps: first, surface micromachining a thin film on a silicon wafer to form the nanochannels; second, etching away the underlying silicon to release the membrane. These nanoporous membranes are engineered to permit the passage of glucose, insulin, and other small metabolic substances, while blocking harmful immune components like macrophages, cytotoxic cells, and complement proteins. The membranes are integrated into a capsule that encloses the islet cells. Because insulin molecules and immune proteins such as IgG differ in size by only a few nanometers, the precise and uniform pore size achieved through micromachining is crucial to ensure both effective immune protection and therapeutic insulin delivery.

6.6.3 Diffusion Chambers

Prolixity Chambers by Debiotech Inc. are drug delivery systems that contain a drug force enclosed by a semipermeable membrane. They are designed to deliver fairly large quantities of medicine, and can indeed accommodate multiple drugs when demanded. Due to the membrane having a face area that is large in proportion to the force, these chambers enable hastily drug release. still, they are generally not intended for long- term use^[28].

6.6.4 Diffusion Controlled Implanted Tubes^[29-33]

These devices utilize a narrow aperture to ensure a slow, sustained release of medication, making them ideal for the long-term administration of highly potent drugssometimes extending over several years. A notable example is the five-year birth control implant, which uses elastomeric tubing^[33]. A similar device is the Duros™ osmotic pump developed by ALZA Corporation. This system is nonbiodegradable and relies on osmotic pressure to deliver small molecules, peptides, proteins, DNA, and other biologically active macromolecules, either systemically or directly to targeted tissues. The DUROS® implant is a tiny cylindrical structure crafted from titanium alloy, designed to safeguard and stabilize the drug formulation within, using ALZA's proprietary technology. Water enters through a semi-permeable membrane at one end of the implant, while the drug is dispensed at a controlled rate from the opposite end, with delivery durations that can extend up to 12 months.

7. Therapeutic application of IDDSs:

7.1 Ocular disease

Several types of implantable systems have been developed to provide sustained ocular drug delivery. These include membrane-controlled devices, implantable infusion systems, and silicone-based implants. One example of a membrane-controlled system is the ocular insert (ocuser), which contains a drug reservoir with pilocarpine base and alginic acid, enclosed within an ethylene-vinyl acetate membrane that regulates drug release^[34,35]. The ocuser delivers pilocarpine at a consistent rate of 20 or 40 µg/h for up to seven days, following an initial burst release. This system has shown good tolerance in adult patients, effectively managing intraocular pressure with minimal side effects. However, it appears to be less well-tolerated among elderly patients, who are the primary group needing such treatment. For ocular cancer



therapy, implantable systems such as silicone rubber balloons loaded with antineoplastic agents have also been investigated^[36-38].

7.2 Contraceptives:

Norplant, a subdermal implant designed for long-term delivery of the contraceptive hormone levonorgestrel, has recently received FDA approval for marketing. The system includes six silicone capsules, each containing approximately 36 mg of levonorgestrel. These capsules are inserted just beneath the skin, typically on the inner side of the upper arm or forearm, using a trocar, and arranged in a fan-like pattern from a single-entry point. Clinical data shows that Norplant users experience a low pregnancy rate fewer than 1.5 per 100 women over four years. After four years, 42% of users continued with the method, indicating a level of acceptance similar to other contraceptive options. Other polymer-based contraceptive systems currently being researched include vaginal rings made of silicone rubber, which are used for periods ranging from 3 to 76 months, often removed for one week each month to allow menstruation; the Progestasert, an intrauterine device made from ethylene-vinyl acetate copolymer that releases hormones for up to a year; and injectable microspheres or rods made from biodegradable polymers^[32].

7.3 Dental application

Polymeric implants have been studied for various dental uses, including the sustained local delivery of fluoride, antibacterial agents, and antibiotics. Stannous fluoride has been incorporated into different dental cements to enable controlled fluoride release over time. In another approach, fluoride was dispersed within a hydrogel made from a copolymer of hydroxyethyl methacrylate and methyl methacrylate, which was coated with an outer layer of the same copolymers in varying ratios to regulate the rate of drug release. This device, approximately 8 mm in length and containing 42 mg of fluoride in its core, was affixed to the buccal surface of the maxillary first molar. It was engineered to deliver fluoride at a rate of 0.5 mg per day for a duration of 30 days^[39-41].

7.4 Cancer

Silicone rod implants, similar to those used for delivering levonorgestrel, have been explored as delivery systems for ethinylestradiol and testosterone propionate in individuals with prostate cancer. Lupron Depot, developed by Takeda Chemical Industries, is an implant-based system that offers a one-month sustained release of leuprolide acetate, a synthetic analog of gonadotropin-releasing hormone (GnRH). This implant consists of biodegradable microspheres made from a 1:1 polylactic-glycolic acid copolymer and contains 10% leuprolide acetate, designed for prostate cancer treatment. Similarly, Zoladex, produced by ICI Pharma, delivers a one-month controlled release of goserelin acetate from a biodegradable implantable rod for managing prostate cancer.

7.5 Other applications

Several insulin delivery systems have been developed and assessed using a biofeedback approach. These systems are designed to control drug release based on the body's real-time need for the medication. From a therapeutic standpoint, they closely mimic the natural secretion patterns of glands like the pancreas. Different strategies have been utilized to achieve self-regulated drug delivery^[32,42]. The examples mentioned above illustrate just a few therapeutic uses of implantable drug delivery systems.

8. Future prospective:

Currently, significant research is underway in the field of implantable drug delivery systems. However, further advancements are still needed, particularly in the development of biodegradable and biocompatible materials, understanding drug release kinetics, and enhancing existing delivery methods before these technologies can be widely applied. Looking ahead, researchers are hopeful that many of these systems will achieve optimal zero-order drug release kinetics in vivo, ensuring consistent drug delivery over extended periods especially beneficial for patients requiring long-term treatment. New medications continue to emerge, with many based on proteins and peptides that are unstable when administered orally. Innovative prolonged-release delivery systems offer the potential to release these



drugs at steady rates over time, eliminating the need for frequent dosing. In the coming years, the advancement of implantable delivery technologies is expected to reduce treatment costs, improve drug efficacy, and boost patient adherence to therapies^[43-45].

II. CONCLUSION

Implantable drug delivery is a promising area in pharmaceutical technology, but it's often overlooked during the development of new drug delivery systems. These technologies can significantly reduce how often patients need to take medication and allow for precise, targeted delivery of drugs to specific areas in the body. Implant-based systems are already being used in various medical treatments, including dental care, eye diseases, and cancer therapy. However, like any material placed inside the body, implants raise important questions about biocompatibility. For instance, the body may form a fibrous layer around the implant, and if the device is designed to break down over time, the by-products from that process must be carefully assessed for any toxic or immune-related reactions.

Another challenge lies in developing user-friendly ways to control these implants from outside the body. For these systems to be truly effective in real-world use, researchers need to create reliable methods to trigger drug release when needed.

Looking ahead, future medications will likely require even more advanced delivery systems, meaning pharmaceutical scientists will face tough but exciting challenges as they work to meet the needs of modern healthcare.

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