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A Comprehensive Review on the Implantable Drug Delivery System

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Abstract: *Historically, medications were primarily administered orally as powders or liquids. However, the oral route often presents limitations, such as poor bioavailability, degradation in the gastrointestinal tract, and variations in absorption. To overcome these issues, alternative dosage forms were developed. Implantable drug delivery systems (IDDS) were designed to meet this need. These implants are solid formulations produced through processes such as extrusion, moulding, or compression, containing a drug intended for localized or systemic release. Implantable devices enable continuous, site-specific drug administration proving particularly valuable in the treatment of conditions such as brain tumours and prostate cancer. IDDS enhance therapeutic efficacy, reduce dosing frequency, minimize side effects, and ensure targeted, constant-rate drug delivery. By improving bioavailability, patient compliance, and therapeutic precision, these systems overcome many limitations of traditional dosage forms.*
This review provides a comprehensive overview of implantable drug delivery systems, focusing on their types, materials, mechanisms of action, advantages, limitations and therapeutic applications.

Keywords: Implantable Drug Delivery System (IDDS), Implants, Drug Delivery, Targeted Therapy, Controlled Release

I. INTRODUCTION

Implantable drug delivery devices are subcutaneous systems specifically engineered to deliver therapeutic agents into the bloodstream without requiring repeated injections [1]. Such systems are completely placed beneath the skin in a discreet and biocompatible manner, allowing for the consistent administration of various therapeutic agents, including insulin, steroids, chemotherapeutics, analgesics, total parenteral nutrition components, and anticoagulants such as heparin[2].

The concept of implantable systems for sustained drug delivery was first proposed by **Lafarge in 1861**, with the earliest practical applications involving solid implants containing steroid hormones that enabled continuous release over time. Implantable drug delivery systems (IDDS) are specifically designed for subcutaneous administration, providing controlled and prolonged release of drugs without the need for frequent injections[3]. An implantable drug delivery system represents a significant advancement in therapeutic technology aimed at increasing drug efficacy and reducing the risks associated with severe diseases such as cancer, ischemic heart disease, stroke, and HIV/AIDS[3]. Despite major advances in drug delivery science, maintaining a consistent therapeutic plasma concentration remains a challenge. Conventional oral or intravenous administration can result in fluctuating drug levels, causing peaks and troughs that may lead to side effects or therapeutic failure. To address this, implantable systems offer a sustained and optimal drug release profile that minimizes such variations[4].Implantation is generally performed through surgical techniques, specialized needles, or insertion devices designed to place the implant in tissues beneath the skin or within muscles.

Implant-based drug delivery systems are situated beneath the skin and may feel like a small nodule or pimple under the surface. Their purpose is to gradually release medication into the bloodstream, eliminating the need for frequent injections. Additionally, this system is particularly advantageous for drugs that degrade in the acidic environment of the stomach or irritate the gastrointestinal tract. It also avoids first-pass metabolism, which can significantly reduce the

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drug's bioavailability[5]. Implantable drug delivery systems are currently utilized for various therapeutic applications, including cancer therapy, dental treatments, and contraception. Moreover, the growing number of implantable devices available on the market reflects the expanding interest and technological advancements in this area of pharmaceutical research.[5].

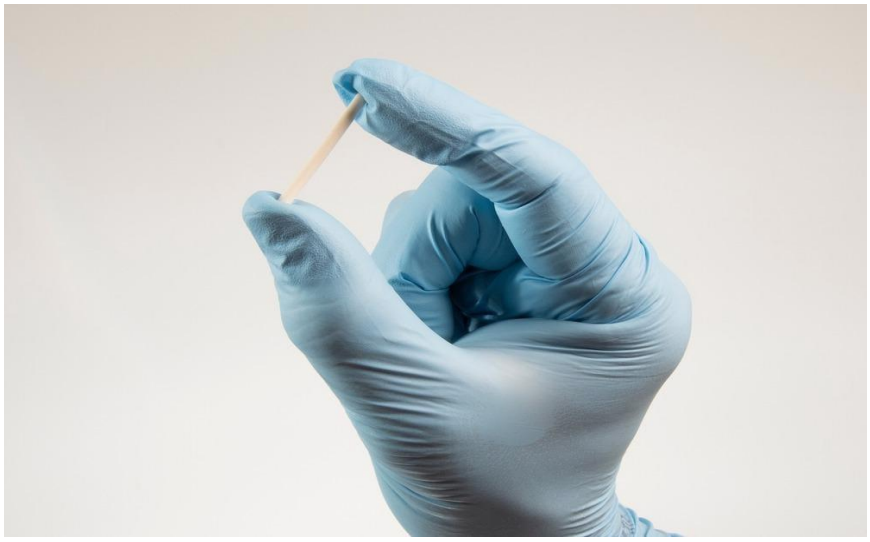

Fig:1 Implantable drug delivery system. [27]

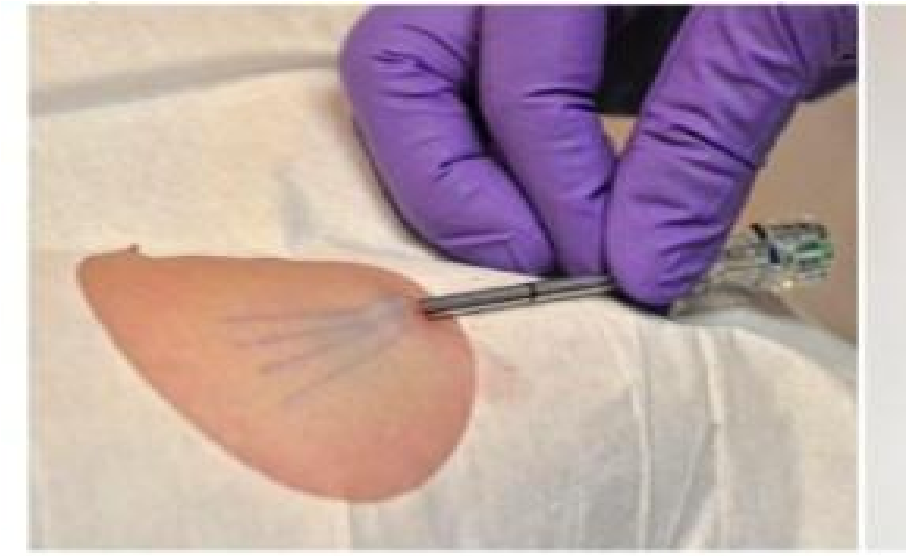

Fig: 2 Implantable drug delivery system [1].

Implant delivery systems are situated beneath the skin and may feel like a small nodule or pimple under the surface. Their purpose is to gradually release medication into the bloodstream, eliminating the need for frequent injections. Additionally, this system is particularly advantageous for drugs that degrade in the acidic environment of the stomach or irritate the gastrointestinal tract. It also avoids first-pass metabolism, which can significantly reduce the drug's bioavailability[5]. Implantable drug delivery systems are currently utilized for various therapeutic applications, including cancer therapy, dental treatments, and contraception. Moreover, the growing number of implantable devices available on the market reflects the expanding interest and technological advancements in this area of pharmaceutical

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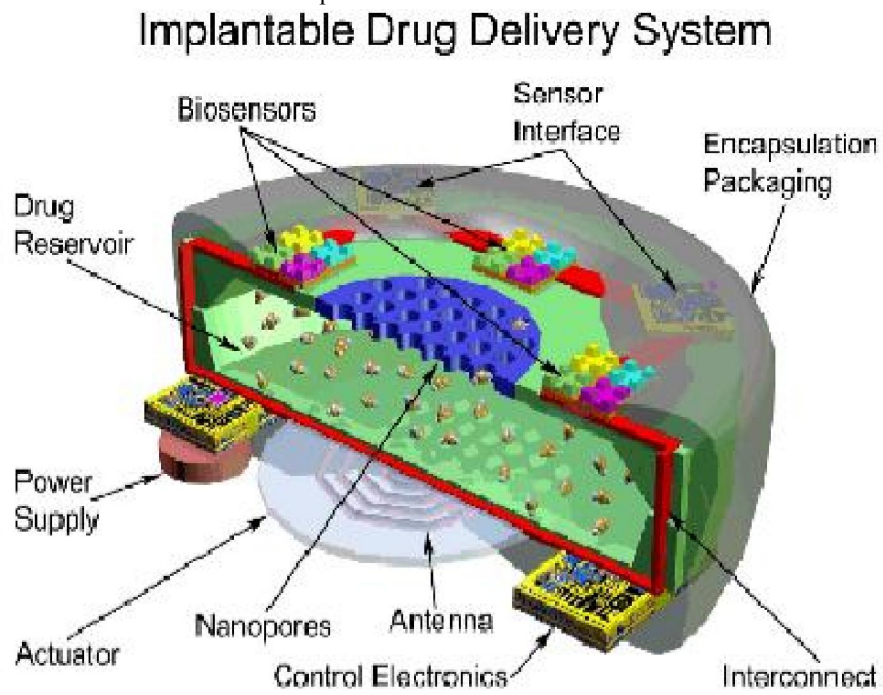

Fig:3 Implantable drug delivery system[30].

- **Ideal Requirements of Implantable Drug Delivery Systems**

Biocompatible to ensure safe interaction and compatibility with body tissues.[4]
Sterile to prevent microbial contamination and infection during use.[8]
Biostable to preserve functionality and integrity within the biological environment .[8]
Non-carcinogenic, ensuring that the material and system do not induce cancer formation.[5]
Easily sterilizable to ensure safety and suitability for clinical applications.[7]

- **Benefits of Implantable Drug Delivery Systems**

Improved therapeutic efficiency and efficacy [8].
A smaller dose achieves the desired pharmacological effect[8].
Minimizes systemic side effects and adverse reactions[1].
Reduces hospital visits and medical supervision requirements[4].
Avoids **first-pass metabolism**, improving bioavailability[7].

- **Limitations of Implantable Drug Delivery Systems**

Potential risk of systemic **toxicity or poisoning** [1].
Invasive and may cause pain or discomfort [10].
Requires **surgical intervention** for device implantation [14].
Risk of **inflammation or infection** at the implant site [13].
High manufacturing and procedural costs [13].

- **Advantages of Implantable Drug Delivery System**

Reduces the **adverse drug effects** [7].
Provides a **highly effective** route of administration [7].

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Avoids **first-pass hepatic metabolism,** enhancing bioavailability [9].
Promotes **better patient compliance** and convenience [8].
Minimizes **drug wastage** due to controlled dosing [9].

● **Disadvantages of Implantable drug delivery system**
Applicable primarily to **highly potent drugs** [3].
May still cause **unwanted side effects or adverse reactions** [5] .
Invasive procedure required for implantation [1].
Limited use to pharmaceuticals with **high potency** and stability [1].
Possibility of **incomplete or insufficient drug release** [5].

● **Classification of Implantable drug delivery system** [6].
`Implantable Drug Delivery Systems`

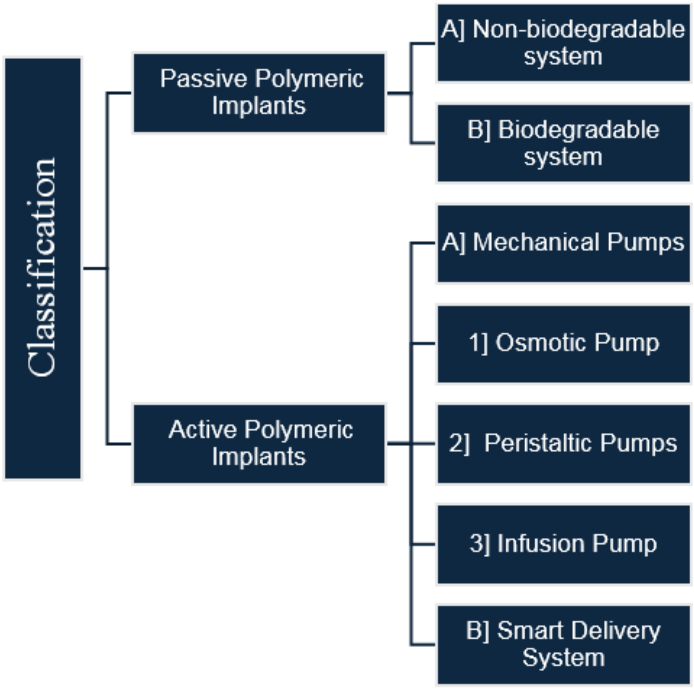

Table : Classification Of Implantable Drug Delivery Sytem .

1) Passive Polymeric Implants
Passive polymeric implants represent one of the fundamental approaches in drug delivery, characterized by their reliance on **intrinsic material properties** and **natural diffusion mechanisms** for drug release [8].Typically; passive implants are composed of simple drug formulations and are generally **uniform, single-unit systems** with consistent structural integrity [9].

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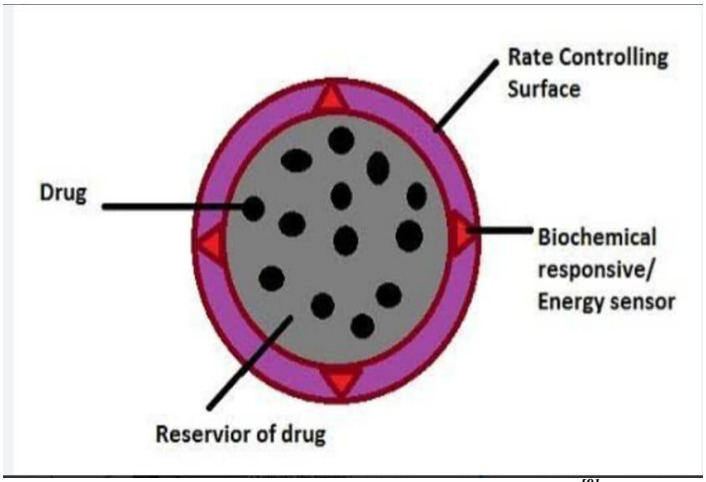

Fig: 4 ***Activated Modulated Drug Delivery System*** [9].

a) Non-Biodegradable Systems

Non biodegradable implants are fabricated using polymers such as **silicones, polyurethanes, polyacrylates**, and copolymers like **polyethylene vinyl acetate (PEVA)**. These implants may exist as **reservoir-type** or **monolithic systems**. In monolithic designs, the drug is **uniformly dispersed throughout a polymer matrix**, allowing controlled diffusion over time [1] .

Common polymers employed in non-biodegradable systems include:

Polyurethanes: Provide excellent mechanical strength and biocompatibility.

Silicone elastomers: Ensure tissue compatibility and enable stable, predictable drug release.

Polyethylene vinyl acetate (PEVA): Facilitates precise control over diffusion rates.

Polyacrylates: Contribute to structural integrity and improved drug retention [8].

Drug release in these systems occurs through **gradual diffusion of the embedded drug molecules**. The **drug concentration** within the polymer base and its **diffusion characteristics** Influence the over all release rate which isoften non- linear . In reservoir type systems , release kinetics are governed by the **thickness and permeability** of the **non-biodegradable membrane** that encapsulates the drug core [4] .

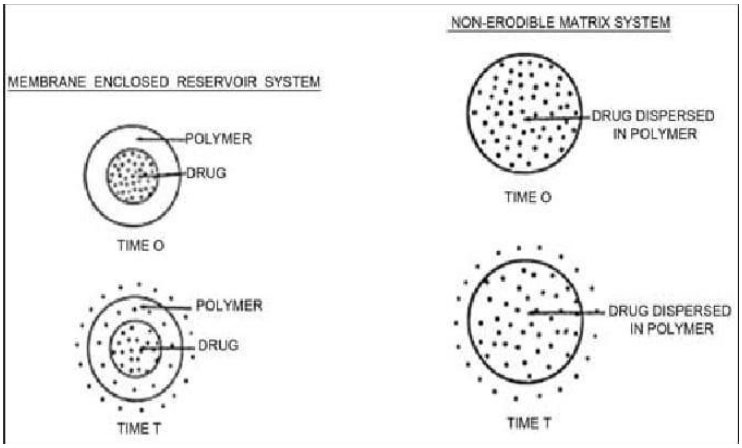

Fig: 5 ***Cross-Sectional View of Non-Erodible Reservoir and Matrix Systems Showing*** .

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Diffusion of Drug across the Polymer [3] **.**

Matrix systems are another widely used form of **non-degradable implants,** where the drug is **evenly distributed throughout a solid polymer matrix.** As the drug diffuses through the **non-degradable polymeric network,** a **sustained-release profile** is achieved [10].

b) Biodegradable Systems

Biodegradable implants are designed to **decompose naturally within the body**, eliminating the need for surgical removal after the treatment period. These systems utilize **biocompatible polymers** that undergo **hydrolytic or enzymatic degradation**, producing **non-toxic by products**. Drug release in biodegradable implants occurs through a combination of **diffusion and polymer erosion** mechanisms [8].

The main biodegradable polymers include: [8]

Polylactic acid (PLA)

Polyglycolic acid (PGA)

Poly(lactic-co-glycolic acid) (PLGA)

Polycaprolactone (PCL)

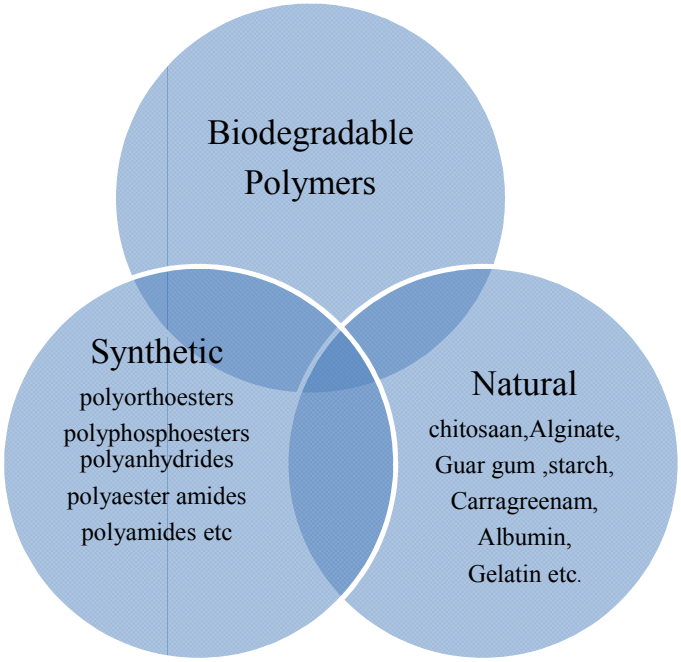

Fig: 6 ***Biodegradable Polymers*** [11] **.**

2) Active Implant Systems

In contrast to passive systems, **active implantable drug delivery systems** offer **superior precision and adaptability** by incorporating **mechanical, electronic, or electrochemical components** that actively regulate the release of therapeutic agents[8].

Such systems are gaining prominence for their ability to deliver medications in a **controlled, programmable, and feedback-responsive manner**, [1] .

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a) Mechanical Pumps

1) OsmoticPumps

Osmotic pump systems generate **osmotic pressure** to drive drug release. This pressure is created by **fluid movement across a semipermeable membrane,** which maintains **consistent drug delivery rates** regardless of physiological variations or drug concentration changes[8].

Various dosage forms have been developed based on osmotic principle to achieve controlled drug delivery from a reservoir system. In such devices, the drug reservoir is enclosed within a semi-permeable membrane, commonly composed of cellulose ester materials. The internal compartment of the system is filled with an osmotic agent, such as sodium chloride (NaCl) or another suitable solute, which serves to maintain osmotic pressure [14].

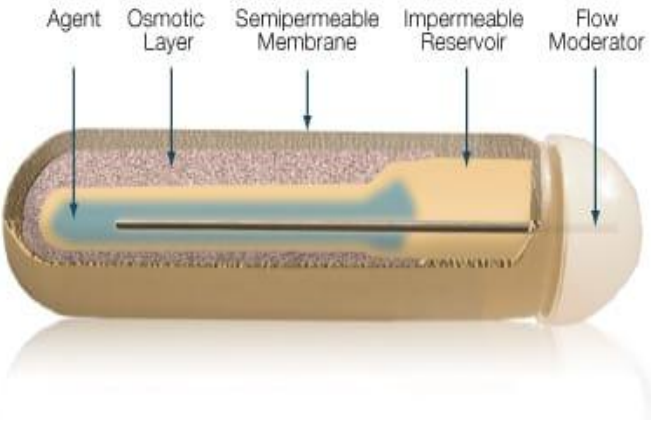

Fig: **7 Osmotic Pumps** [13].

2) Peristaltic Pump

Peristaltic pumps are primarily rotary solenoid-driven systems designed for precise and continuous drug delivery. The key components pump, electronic circuitry, and batteries—are securely enclosed within titanium chambers that are hermetically sealed through laser welding. To enhance biocompatibility and minimize tissue reactions, these chambers are coated with a layer of silicone polymer [14].

These rotary solenoid-driven pumps are typically powered by an external energy source, most often a rechargeable battery. Peristaltic systems, including implantable infusion pumps, are designed for long-term use and can function effectively for several years, depending on their energy source and mechanical integrity. The refilling process occurs via a silicon rubber septum, ensuring sterility and ease of maintenance. One of the notable advantages of this system is the ability to regulate the rate of drug administration through an external remote control, allowing precise and adaptable dosage management [15].

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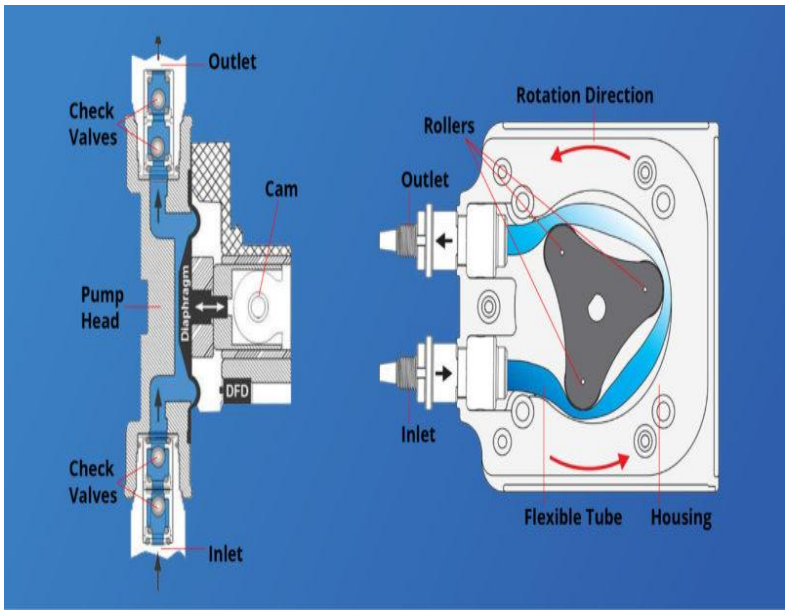

Fig:8 Peristaltic Pump [16].

3) Infusion Pump

The infusion pump represents one of the earliest fully implantable, mechanically controlled drug delivery systems that achieved commercial application[14].These devices utilize fluorinated hydrocarbons as an internal energy source to propel the stored drug within the body. Historically, they were extensively used for the controlled administration of insulin in diabetic patients [17].

The first compartment serves as the energy chamber, while the second stores the drug formulation. Upon activation, the pressurized gas in the energy chamber expands, exerting pressure on the diaphragm and pushing the drug through a calibrated orifice equipped with a flow regulator. This mechanism ensures steady and accurate drug delivery at a predetermined temperature, without the need for an external power source [4].

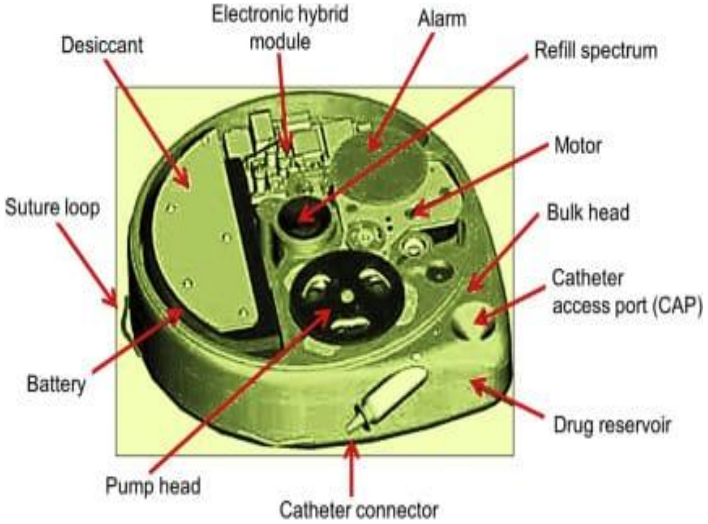

Fig:9 Infusion Pump [18].

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Mechanism of Implantable Drug Delivery Systems

Implantable drug delivery systems primarily operate through four fundamental mechanisms: **osmotic pumping, matrix degradation, controlled swelling, a**nd **passive diffusion**. In controlled swelling systems, drug molecules are released as the polymer matrix absorbs fluid and expands. This swelling process restricts solvent penetration, thereby reducing the rate of drug release and allowing sustained delivery [19].

The rate of drug release in swelling-based systems is largely governed by the extent and rate of solvent penetration into the polymer matrix. Since solvent diffusion often occurs slower than the drug's molecular diffusion, these systems tend to exhibit prolonged release profiles. In addition, partial matrix degradation can complement diffusion, enhancing the system's performance [20].

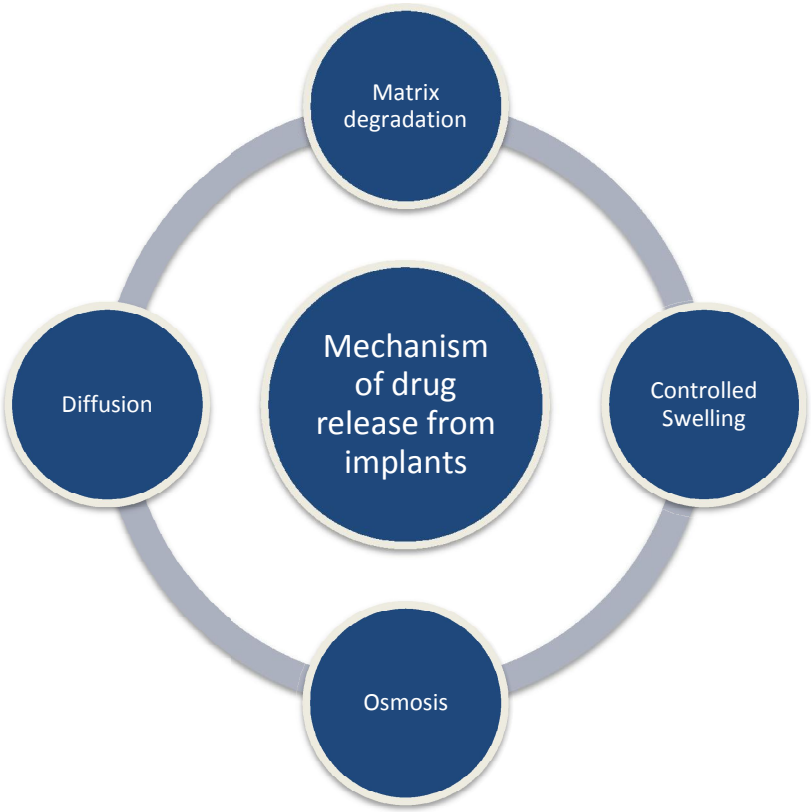

Fig :10 Categories of mechanism of drug release from implantable system [21,19].

1) Matrix Degradation

Matrix degradation refers to the incorporation of a drug into a biodegradable polymer matrix that undergoes decomposition within the body through enzymatic or hydrolytic activity. Upon degradation, the drug is released and diffuses into the surrounding tissues. Polymers such as **poly(lactic-co-glycolic acid) (PLGA)** and **polyanhydrides** are commonly used due to their predictable degradation rates and excellent biocompatibility. This mechanism is effectively utilized in **biodegradable contraceptive implants** for sustained drug release without surgical removal and in **Gliadel wafers** for localized chemotherapy[19].

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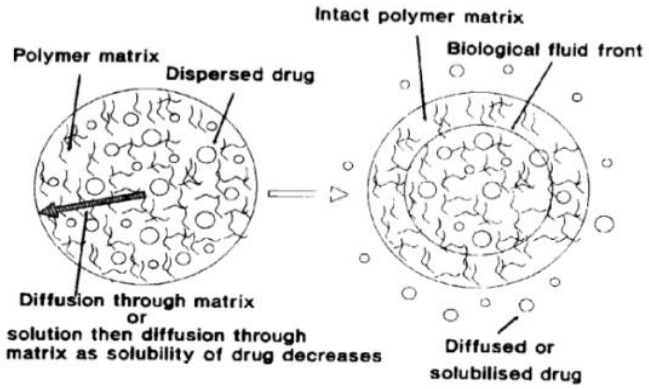

Fig: 10 Matrix Degradation System [22] .

2) Controlled Swelling

In swelling controlled systems,the drug is uniformly dispersed or dissolved within a polymer matrix through which it cannot freely diffuse. When the polymer comes in contact with biological fluids,it swells,allowing the entrapped drug to be released at a regulated rate .Thus, the release rate is primarily governed by the diffusion rate of the fluid into the polymer matrix.These systems enable a predictable and sustained release profile ideal for long-term therapeutic application [19].

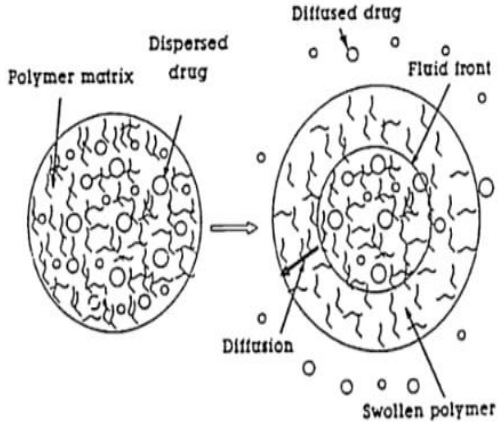

Fig: 11 Swelling Controlled Polymeric Drug Delivery System [24].

3) Diffusion

In diffusion-controlled systems, drug molecules migrate from regions of higher concentration to regions of lower concentration, driven by a **concentration gradient**. This natural process facilitates the gradual and controlled release of drugs from the polymeric matrix. The diffusion mechanism can occur through the polymer (reservoir system) or through the pores formed within the matrix (matrix system), ensuring consistent and prolonged delivery [19] .

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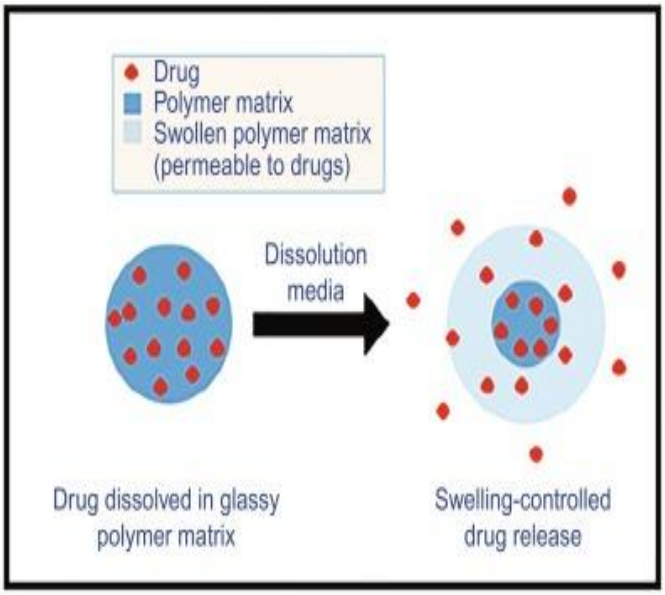

Fig:12 Diffusion Mechanism [25] .

4) Osmosis

Osmotic-controlled systems encapsulate the drug within a **semipermeable membrane** that permits water entry but restricts drug escape. As water penetrates the system, osmotic pressure builds up inside, forcing the drug solution out through a small orifice. This process ensures **precise, continuous, and controlled drug release** over an extended period, independent of external environmental conditions. Osmotic systems are widely employed in **implantable devices** for their reliability and steady pharmacokinetic profiles [21] .

Approaches of implantable drug delivery system

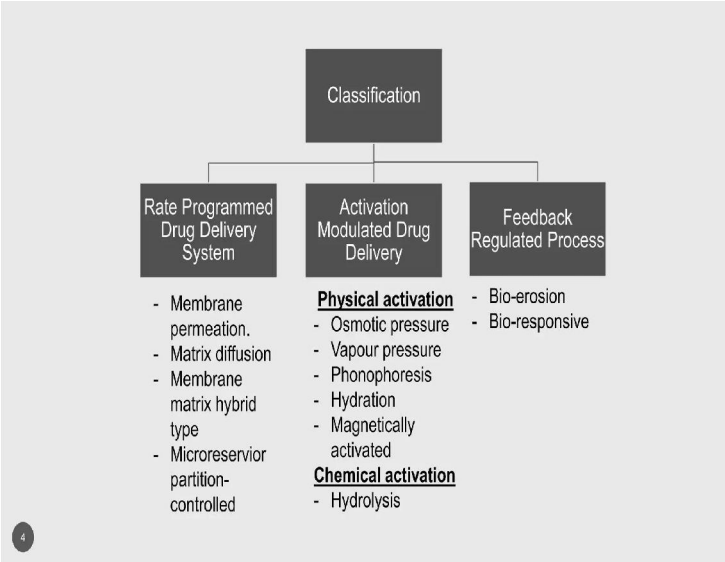

Table :2 Approaches of Implantable Drug Delivery System [26] .

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Therapeutic Applications of Implantable Drug Delivery Systems

1) **Immunization**

Compared to antibiotics, polymeric plant chemicals have been shown to offer superior disease prevention [28].

2) Narcotic Antagonists

Naltrexone has been thoroughly assessed in implants from longterm opioid antagonist delivery. For extended narcotic a ntagonist action. [29] .

3)Cancer

With silicone rod implants, prostate cancer can be successfully treated by giving ethinyl oestradiol and testosterone pro pionic acid [32].

4) Diabetes

Diabetes is a chronic disease in which implantable systems can greatly improve both diagnosis and treatment [33] .

5)Other Applications

Numerous insulin administration methods have been developed, assessed, and previously documented for a biofeedbac k technique. The drug release rate in thesebiofeedbackcontrolled systems depends on the body's need for the medication at a given moment [34].

Recent Research Drugs in Implantable Drug Delivery Systems.

Drug	Implant type / method	Main clinical / research uses
Carmustine	Biodegradable polymer wafer (polifeprosan with carmustine) implanted in tumour cavity at neurosurgery	Local chemotherapy for high-grade glioma / malignant glioma [35].
Leuprolide acetate	Subcutaneous long-acting	Long-term GnRH agonist release for prostate cancer [12].
Buprenorphine	Subdermal polymer implant rods	Long-acting maintenance therapy for opioid-use disorder [36].
Insulin	Fully implantable insulin pump / intraperitoneal or intrathecal pump systems .	Long-term continuous insulin delivery (type 1 diabetes) [37].
Dexamethasone	Biodegradable intravitreal implant	Treatment of macular edema, non-infectious posterior uveitis, branch retinal vein occlusion (ocular sustained release) [38] .
Fluocinolone acetonide	Non-biodegradable intravitreal implant (long-duration insert)	Chronic diabetic macular edema and other retinal conditions [39] .
Intrathecal	Implantable programmable infusion pump	Chronic refractory cancer and noncancer pain management (lower systemic doses) [40].

Table : 3 Recent Research Drugs in Implantable Drug Delivery Systems.

II. CONCLUSION

Implantable drug delivery systems provide controlled, long-term, and targeted drug release, improving therapeutic effectiveness and patient compliance. They overcome limitations of conventional dosage forms and offer sustained drug levels, though they require surgical procedures and careful design to ensure safety and performance.

Implantable Drug Delivery Systems (IDDS) have emerged as one of the most promising and innovative approaches in modern therapeutics, offering controlled, sustained, and site-specific drug administration. implants has significantly enhanced therapeutic efficacy while minimizing systemic side effects and improving patient compliance.

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