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Implantable Drug Delivery Devices, Long-Acting Injectables, and Implants: An Emerging Paradigm in Pharmaceutical Therapy

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ABSTRACT :

Advances in pharmaceutical technology have transformed conventional drug administration methods into more sophisticated and patient-compliant approaches. Among these, implantable drug delivery devices, long-acting injectables, and implants have gained significant attention due to their ability to provide sustained, controlled, and targeted drug release over extended periods. These systems reduce dosing frequency, improve therapeutic adherence, and optimize pharmacokinetic profiles. Such innovations are particularly valuable in chronic conditions, oncology, hormonal therapies, and infectious diseases like HIV and tuberculosis. This review provides an overview of the evolution, design strategies, mechanisms, clinical applications, and future prospects of implantable devices and long-acting formulations. Challenges including biocompatibility, manufacturing complexity, cost, and regulatory barriers are also discussed. Overall, implantable and long-acting systems represent a promising frontier in achieving precision and personalized medicine.

Keywords: Implantable devices, long-acting injectables, drug delivery systems, controlled release, implants, sustained release, biocompatibility, personalized medicine.

1. Introduction

The pharmaceutical industry has continuously sought to improve therapeutic outcomes by maximizing drug efficacy while simultaneously minimizing dosing frequency, adverse effects, and patient burden. Conventional routes of drug administration such as oral, intravenous, and intramuscular delivery remain the cornerstone of therapy for most diseases; however, they are often constrained by significant limitations. Oral delivery, despite being the most convenient and widely accepted route, is frequently hindered by challenges such as poor solubility of active pharmaceutical ingredients, variable gastrointestinal absorption, extensive first-pass metabolism, and the necessity for multiple daily dosing regimens to sustain therapeutic levels. Similarly, parenteral delivery routes, while capable of bypassing metabolic barriers, are associated with issues of patient discomfort, injection-site reactions, the requirement for healthcare supervision, and limited duration of action of the administered drug. These drawbacks collectively contribute to fluctuating plasma drug concentrations, reduced bioavailability, poor disease management, and, most critically, poor patient adherence in chronic therapies.

To address these challenges, significant attention has been directed toward the development of advanced drug delivery systems, particularly implantable drug delivery devices and long-acting injectables (LAIs). These innovative platforms are designed to provide sustained, controlled, and targeted release of therapeutic agents over extended periods of time, ranging from weeks to months, and in some cases, several years. Such systems ensure that plasma drug concentrations are maintained within the desired therapeutic window, thereby avoiding the peaks and troughs commonly seen with conventional dosage forms. This not only enhances pharmacological efficacy but also reduces the risk of dose-related toxicity and subtherapeutic drug levels.

From a clinical perspective, long-acting and implantable systems are of paramount importance in managing conditions that demand continuous or prolonged therapeutic exposure. Chronic diseases such as diabetes mellitus, cancer, cardiovascular disorders, and psychiatric illnesses often require strict adherence to long-term medication schedules, which is difficult to achieve with conventional dosing regimens. Similarly, areas such as contraception, infectious disease management (e.g., HIV, tuberculosis), and hormone replacement therapy benefit immensely

from controlled-release implants and injectables, as they reduce the dependency on patient memory and compliance. Moreover, in oncology, implantable devices can facilitate localized drug delivery directly to tumor sites, thereby improving therapeutic efficacy while limiting systemic toxicity.

In addition to patient-centric benefits, these technologies also offer broader healthcare advantages. By improving adherence, reducing hospitalization due to treatment failure, and lowering the overall drug burden, they contribute to enhanced healthcare outcomes and potentially reduced economic costs. Advances in polymer science, nanotechnology, and material engineering have further propelled the design of implantable and injectable systems, enabling the incorporation of both small molecules and biologics, including peptides, proteins, and monoclonal antibodies, into long-acting formulations.

Therefore, implantable drug delivery devices and long-acting injectables represent an emerging paradigm in pharmaceutical therapy, combining engineering innovation with clinical necessity. Their ability to sustain controlled drug release, improve patient adherence, and optimize therapeutic outcomes positions them at the forefront of modern drug delivery research and development. As the demand for more efficient and patient-friendly therapeutic strategies continues to rise, these systems are expected to play an increasingly pivotal role in the future of medicine[1-2].

2. Historical Background

The concept of implantable drug delivery dates back to the 1930s, when the first non-degradable pellets for hormone therapy were developed[3]. The 1970s marked a revolution with the introduction of polymer-based implants capable of sustained release. Over time, advances in biodegradable polymers such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA) enhanced the safety profile of such devices[4]. In parallel, long-acting injectables, including oil-based suspensions and depot formulations, became an integral part of psychiatric and contraceptive therapies[5]. Today, modern implants combine drug release kinetics with biocompatibility, imaging compatibility, and in some cases, remote control of release via external stimuli[6].

3. Classification of Implantable Drug Delivery Systems

Implantable devices can be broadly classified into:

- Non-biodegradable implants – made of silicone or EVA (ethylene-vinyl acetate), requiring surgical removal after drug exhaustion[7].
- Biodegradable implants – composed of polymers like PLA, PLGA, and PCL (polycaprolactone), which degrade naturally after drug release[8].
- Osmotic pumps – such as the DUROS® system, which provide zero-order drug release by osmotic pressure[9].
- Hydrogel-based implants – swellable networks that modulate drug release through diffusion[10].

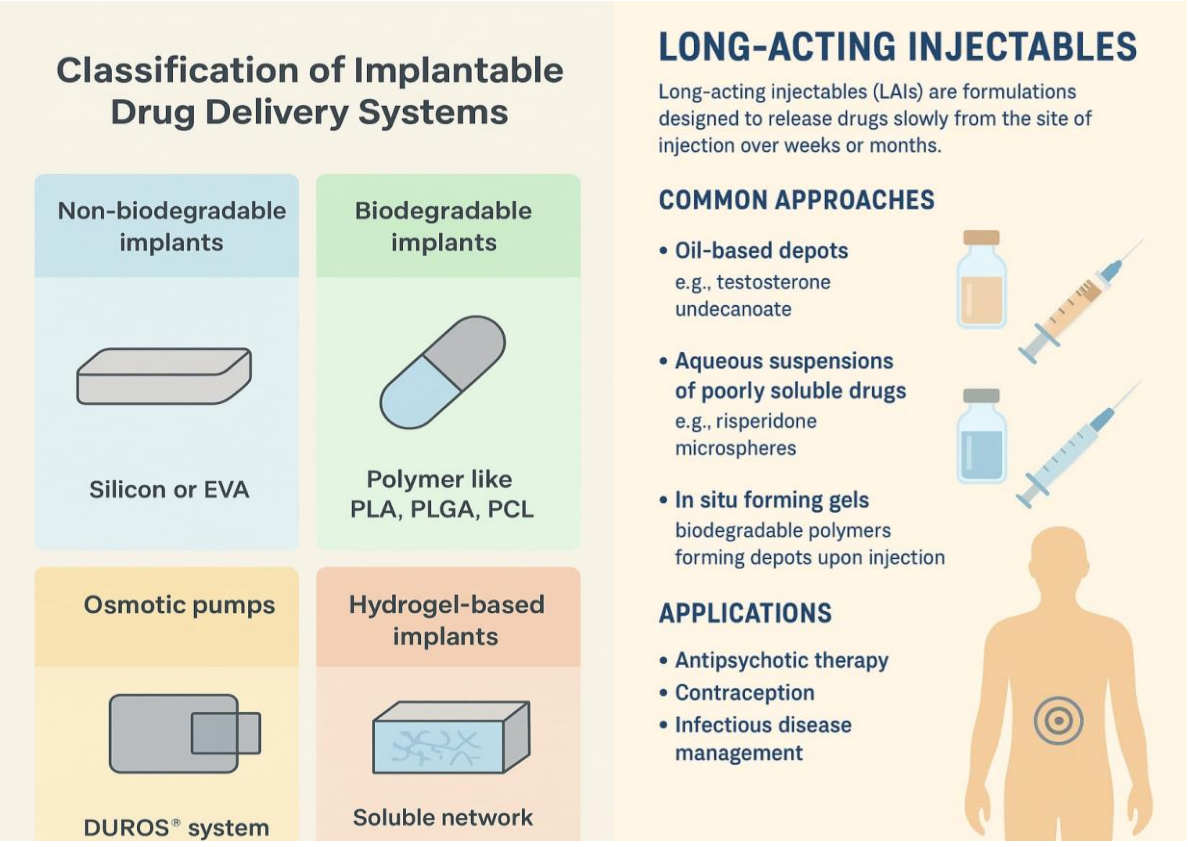

Fig.no 1: Classification of Implantable Drug Delivery Systems and Long Acting Injectables with its applications.

4. Long-Acting Injectables (LAIs)

Long-acting injectables (LAIs) are specially designed parenteral formulations that allow a sustained and controlled release of drugs from the site of injection, thereby maintaining therapeutic drug levels for prolonged periods ranging from several weeks to even months. This minimizes the need for frequent dosing and helps improve patient compliance and adherence to therapy. The release of the active pharmaceutical ingredient is controlled either by the physicochemical properties of the drug, the formulation vehicle, or the use of specialized delivery systems. The major approaches for developing LAIs include:

- **Oil-based depots**: Drugs are dissolved or suspended in oily vehicles such as sesame oil or castor oil, which slow down their absorption from the injection site. A typical example is testosterone undecanoate, used in hormone replacement therapy.
- **Aqueous suspensions of poorly soluble drugs**: In this approach, drugs with low water solubility are formulated as micro- or nanoparticles that gradually dissolve in the body fluids after injection. A well-known example is risperidone microspheres, used in the management of schizophrenia.
- **In situ forming gels**: These involve the use of biodegradable polymers that remain in liquid form during injection but solidify or form a gel-like depot once inside the body. This depot then slowly releases the drug over time. Such systems represent an advanced strategy in controlled drug delivery[11].

LAIs are of particular importance in conditions where long-term therapy is needed and non-adherence to medication is a major concern. They are widely applied in:

- **Antipsychotic therapy**, where maintaining constant drug levels helps prevent relapse of schizophrenia or bipolar disorder.
- **Contraception**, where LAIs such as depot medroxyprogesterone acetate provide effective long-term birth control.
- **Infectious disease management**, for instance in tuberculosis and HIV therapy, where maintaining consistent plasma concentrations enhances treatment effectiveness and reduces resistance[12].

5. Mechanisms of Drug Release

The process of drug release from long-acting injectables (LAIs) and implantable systems is governed by a combination of physicochemical and biological mechanisms. These mechanisms determine the rate, duration, and consistency of therapeutic action. The major release mechanisms include:

- **Diffusion-controlled release** – In this mechanism, drug molecules migrate from the polymeric matrix to the surrounding biological fluids primarily through passive diffusion. The rate of release is influenced by factors such as the polymer's porosity, drug solubility, and molecular weight. This pathway often results in a sustained, concentration-dependent release profile[13].
- **Degradation-controlled release** – Here, the drug release is predominantly regulated by the chemical or enzymatic breakdown of the polymer matrix. As the biodegradable polymer undergoes hydrolysis or enzymatic erosion, it gradually loses structural integrity, thereby enabling drug molecules to be liberated at a predictable rate. This provides a controlled and often prolonged delivery of the therapeutic agent[14].
- **Swelling-controlled release** – In hydrogel-based systems, drug liberation is initiated when the polymer absorbs water from the surrounding tissue fluids and swells. This expansion increases the mesh size of the polymer network, allowing drug molecules to diffuse more freely. Such systems enable tunable release profiles depending on the degree of cross-linking and the hydrophilicity of the polymer[15].
- **Osmotically driven release** – In this approach, semipermeable membranes are employed to regulate fluid ingress into the system, generating osmotic pressure that pushes the drug out through a delivery orifice. This design can achieve near zero-order kinetics, thereby maintaining a consistent plasma drug concentration over an extended period[16].

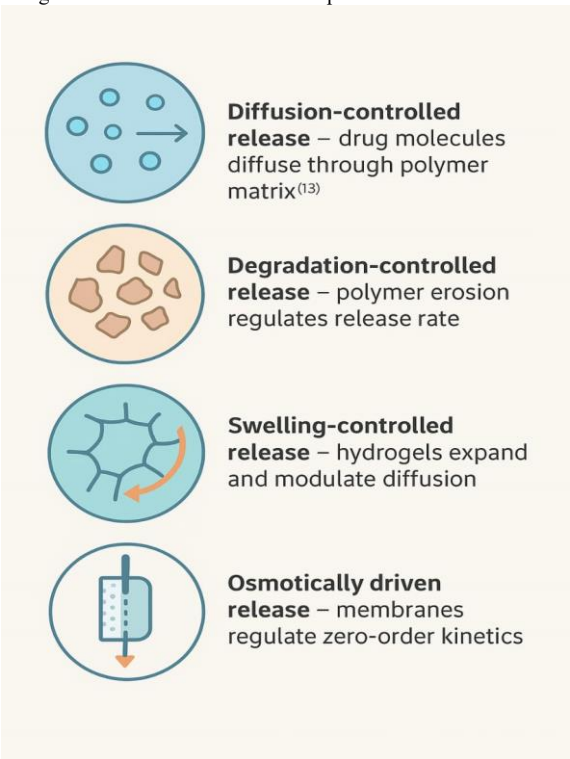

Fig.no 2: Mechanisms of Drug Release

6. Clinical Applications

Implantable drug delivery systems and long-acting injectables (LAIs) have moved beyond experimental concepts and are now playing critical roles in diverse therapeutic areas. Their ability to maintain sustained plasma drug levels, minimize dosing frequency, and improve adherence makes them particularly valuable in chronic and life-threatening conditions. Several key clinical applications include the following.

Oncology:

In cancer therapy, localized delivery of chemotherapeutic agents through implantable devices offers a significant advantage by reducing systemic toxicity and improving drug concentration at
the tumor site. A prime example is the Gliadel® wafer, a biodegradable polymer implant loaded with carmustine (BCNU), which is placed directly into the brain cavity following surgical resection of glioblastoma multiforme. This localized approach ensures high concentrations of the drug in the tumor microenvironment while minimizing systemic exposure, thereby reducing adverse effects typically associated with systemic chemotherapy. Moreover, other experimental implantable systems are being developed to deliver drugs such as paclitaxel and doxorubicin directly to solid tumors, with the aim of achieving sustained drug release over several weeks or months[17].

Contraception:

One of the most widely recognized applications of implantable systems is in long-term contraception. Subdermal implants such as Norplant® and its successor Nexplanon® release progestins at controlled rates, offering contraceptive efficacy for up to three years. These devices not only provide long-term pregnancy prevention but also eliminate user-dependent factors that often compromise the effectiveness of oral contraceptives. Their high success rates, reversibility upon removal, and minimal systemic side effects have made them an important choice for women's reproductive health, particularly in settings where compliance with daily oral contraceptives is challenging[18].

Psychiatry:

Medication non-adherence is a major barrier in the management of chronic psychiatric disorders such as schizophrenia and bipolar disorder. Long-acting injectable antipsychotics, including risperidone microspheres, paliperidone palmitate, and aripiprazole depot formulations, ensure steady plasma drug levels and significantly reduce relapse rates compared to oral therapy. By delivering the drug over weeks or months, LAIs reduce the burden of daily medication and enhance therapeutic outcomes. This strategy also provides clinicians with a reliable means of monitoring adherence, which is often a challenge in psychiatric populations[19].

Infectious Diseases:

Long-acting formulations are transforming the treatment landscape for infectious diseases, particularly in HIV therapy. The combination of cabotegravir and rilpivirine, administered intramuscularly as a monthly or bi-monthly injection, has demonstrated effectiveness in both treatment and pre-exposure prophylaxis (PrEP). This approach reduces the stigma and challenges associated with daily oral antiretroviral therapy (ART), while maintaining consistent viral suppression. These formulations are particularly beneficial for patients in low-resource settings and for those who struggle with adherence to daily regimens, representing a major step forward in global HIV management[20].

Diabetes:

In the field of metabolic disorders, efforts are underway to develop implantable systems capable of delivering insulin or glucagon-like peptide-1 (GLP-1) receptor agonists in a sustained manner. Such systems could alleviate the burden of multiple daily injections in diabetic patients and provide tighter glucose control by mimicking physiological hormone release. Preclinical studies have demonstrated promising outcomes with biodegradable polymer-based implants and encapsulated cell systems designed to secrete insulin in response to glucose levels. These innovations aim to improve not only glycemic control but also patient quality of life[21].

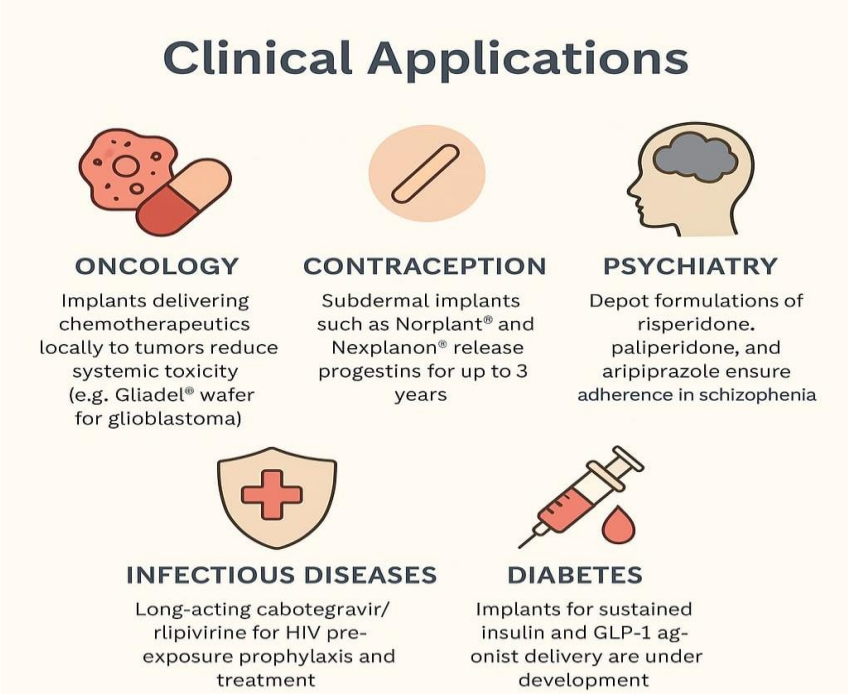

Fig.no 3: Clinical Applications of Implantable drug delivery systems and long-acting injectables

Implantable drug delivery systems and long-acting injectables

7. Advantages

Implantable drug delivery devices and long-acting injectables provide several unique benefits that distinguish them from conventional dosage forms.

- **Improved patient compliance by reducing dosing frequency**: Since these systems release drugs over extended periods ranging from weeks to years, they eliminate the need for daily or frequent dosing. This is particularly beneficial in chronic conditions such as schizophrenia, HIV, or hormonal therapies, where non-adherence is a major barrier to treatment success. By reducing the pill burden, patients are more likely to remain on therapy consistently, leading to better clinical outcomes and reduced risk of relapse or disease progression[22].
- **Steady plasma concentration minimizing fluctuations and side effects**: Conventional oral or injectable drugs often produce "peak and trough" plasma levels that may either fall below therapeutic thresholds or rise to toxic levels. Long-acting implants and injectables maintain drug concentrations within a narrow therapeutic window for prolonged durations. This stable release profile reduces adverse effects, enhances tolerability, and ensures consistent pharmacological activity[23].
- **Enhanced bioavailability of poorly soluble drugs**: Many therapeutic molecules, particularly lipophilic and high-molecular-weight drugs, suffer from poor solubility and limited oral absorption. Implantable systems bypass the gastrointestinal tract and hepatic first-pass metabolism, allowing drugs to be delivered directly into systemic circulation or targeted tissues. This leads to higher bioavailability, reduced dose requirements, and optimized therapeutic effects[24].
- **Targeted/local delivery minimizing systemic exposure**: Implants can be placed at or near the site of disease, allowing high drug concentrations to reach the target tissues while minimizing systemic exposure. For example, chemotherapy wafers implanted in the brain after glioblastoma surgery deliver potent doses directly to the tumor bed with significantly lower systemic toxicity. Similarly, contraceptive implants release hormones locally, reducing systemic hormonal fluctuations[25].

8. Challenges and Limitations

Despite the clear benefits, several challenges limit the widespread use and acceptance of implantable drug delivery systems and long-acting injectables.

- **Surgical insertion and removal (in case of non-biodegradable implants)**: Non-biodegradable systems require minor surgical procedures for implantation and eventual removal once the drug is depleted. This can be inconvenient, costly, and uncomfortable for patients. Surgical intervention also carries risks of pain, scarring, and tissue damage[26].
- **Risk of infection and foreign body response**: The introduction of a foreign material into the body always carries a risk of infection at the implant site. Furthermore, the immune system may recognize the implant as foreign, leading to inflammation, fibrosis, or encapsulation. These biological responses can impair drug release kinetics and reduce device performance[27].

- **Manufacturing complexity and high cost**: The design and fabrication of implants demand sophisticated technologies, strict sterilization, and biocompatible materials. This increases manufacturing costs compared to conventional dosage forms such as tablets or capsules. Cost barriers may limit accessibility, particularly in resource-limited healthcare settings[28].
- **Regulatory hurdles and long approval timelines**: Since implants and LAIs combine aspects of both drugs and medical devices, they undergo rigorous regulatory evaluations for safety, efficacy, biocompatibility, and long-term stability. These processes extend development timelines and increase the overall cost of bringing products to market[29].
- **Dose inflexibility once implanted**: A key limitation of implants is that once placed in the body, the drug release rate cannot be easily modified. If adverse reactions occur or dose adjustments are needed, the implant must often be surgically removed. This lack of flexibility is particularly challenging in therapies requiring dynamic dose titration[30].

9. Future Perspectives

Future research is focused on smart implants that respond to external stimuli such as pH, enzymes, temperature, or even wireless signals to control drug release[31]. The integration of nanotechnology, biodegradable polymers, and microelectronics may allow real-time monitoring and adjustable dosing[32]. Additionally, personalized medicine approaches can optimize implantable systems for patient-specific pharmacokinetic needs[33].

10. Conclusion

Implantable drug delivery devices and long-acting injectables represent a significant leap in pharmaceutical technology. Their ability to ensure prolonged therapeutic effects, minimize dosing frequency, and improve patient adherence makes them invaluable in chronic and life-threatening diseases. Despite existing limitations, ongoing innovations promise to make these systems safer, more effective, and accessible. As the field advances, implantable and long-acting formulations are expected to become central pillars of personalized medicine and next-generation drug delivery.

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