International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2271-2276 www.ijprajournal.com ISSN: 2456-4494

Biodegradable Implantable Drug Delivery System

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Date of Submission: 28-06-2025 Date of Acceptance: 08-07-2025

ABSTRACT: Conventional drug delivery routes are commonly used due to their ease of administration and systemic effects. However, they present significant limitations such as hepatic first-pass metabolism, gastrointestinal degradation, hypersensitivity reactions, low bioavailability, and fluctuating plasma drug levels. These drawbacks reduce patient compliance, especially in chronic therapies.

To address these issues, implantable polymeric drug delivery systems offer controlled and sustained drug release from devices implanted in the body. While non-biodegradable implants require surgical removal and show poor compatibility with water-soluble or highly ionized drugs and macromolecules, biodegradable systems overcome these challenges. They degrade within the body via enzymatic or chemical processes, eliminating the need for removal and enabling better release control.

Recent advances include shape memory-based implants, 3D-printed systems, biosensor integration, real-time monitoring, and personalized medicine, further enhancing the efficiency and precision of drug delivery.

Key words: Hepatic first pass metabolism, conventional drug delivery routes, hypersensitivit reactions, Enzymatic and chemical process,3-D printed system, biosensors,

I. INTRODUCTION :

Implants are small, sterile, solid drug delivery systems composed of highly purified therapeutic agents, typically prepared through methods such as compression, molding, or extrusion. These devices are designed for implantation into subcutaneous or intramuscular tissues via minor surgical procedures or insertion using a large-bore needle.

The primary objective of implantable systems is to provide sustained and controlled drug release into systemic circulation over extended periods, eliminating the need for frequent dosing and repeated needle insertions. This method is particularly suitable for delivering drugs like insulin, steroids, chemotherapeutics, antibiotics, analgesics, heparin, and agents used in total parenteral nutrition.

Implants offer targeted and localized drug delivery, potentially achieving therapeutic effects at lower systemic drug concentrations. Moreover, they bypass first-pass hepatic metabolism and gastrointestinal degradation, significantly improving the bioavailability of drugs compared to conventional oral or injectable routes.

Conventional drug delivery systems often present multiple limitations. Like Oral routes are hindered by harsh gastric environments , enzymatic degradation, hepatic first-pass metabolism, and interference by gut microflora—all of which reduce drug absorption and efficacy. Additionally, for chronic diseases, frequent oral dosing can result in poor patient compliance.

On the other side Parenteral administration, while providing rapid and complete systemic absorption, is invasive, requires trained personnel, and often necessitates repeated injections due to rapid drug clearance, further diminishing patient adherence in long-term therapies.

Implantable drug delivery systems address these challenges by maintaining steady plasma drug concentrations through controlled and prolonged release, enhancing therapeutic outcomes and improving patient compliance, especially in chronic disease management.

According to the World Health Organization (WHO, September 2023), non-communicable diseases (NCDs)—notably cardiovascular diseases, cancers, and diabetes—account for approximately 74% of global deaths. With the increasing burden of chronic diseases, the demand for precise and long-term therapeutic strategies is growing, driving the adoption of implantable drug delivery technologies.

The global implantable drug delivery market was valued at USD 27.2 billion in 2023, with projections indicating significant growth to USD 41–47 billion by 2030–2031, reflecting a

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robust interest in these systems for sustained and targeted drug therapy.

Biodegradable implants in drug delivery: Biodegradable polymers are essential materials in drug delivery systems, designed to degrade within the body through two primary mechanisms: bioerosion and biodegradation. Bioerosion involves the slow dissolution of the polymer matrix, while biodegradation occurs through chemical or enzymatic processes. In some instances, particularly with natural polymers such as albumin, both bioerosion and enzymatic degradation can occur simultaneously.

These polymers can be broadly categorized into natural and synthetic types. Natural polymers, including chitosan, gelatin, alginate, and collagen, are valued for their biocompatibility.

Synthetic polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL), offer tunable properties. Among these, PLGA is the most extensively used synthetic polymer due to its customizable degradation rate and its approval by the Food and Drug Administration (FDA).

When we talk about the Mechanisms of Bioerosion so Bioerosion can proceed in two distinct ways: bulk erosion and surface erosion.

Bulk Erosion: Also known as homogeneous erosion, bulk erosion is characterized by degradation occurring at a nearly uniform rate throughout the entire polymer matrix. This happens when water penetration into the material is faster than the rate of polymer degradation. Consequently, the implant weakens internally before any significant changes are visible on the surface. This can potentially lead to a sudden structural collapse and a "burst release" of the encapsulated drug. Polymers that typically exhibit bulk erosion include poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA).

Surface Erosion:Termed heterogeneous erosion, surface erosion involves degradation that is confined to the surface of the implant. This mechanism occurs when the rate of polymer degradation is faster than the rate at which water can penetrate the bulk of the material. As a result, the implant gradually thins over time while maintaining its structural integrity. This allows for a controlled and predictable drug release profile. Examples of polymers that undergo surface erosion include polyanhydrides and poly(ortho esters).

Bulk erosion and surface Erosion with time :

bservation: The most striking visual difference is the mode of degradation. The bulk-eroding implant undergoes an "inside-out" degradation, leading to a sudden failure. In contrast, the surface-eroding implant degrades in an "outside-in" fashion, with a predictable reduction in size.

All systemtic classes of implImplantable drug delivery system:

IDDS can be broadly categorized into two principal types based on their operational mechanisms: Passive Depot Systems and Active Infusion Devices.

1. Passive Depot Systems:

Passive depot systems rely on inherent physicochemical processes for drug release, without the need for external energy sources or mechanical actuation. Drug release kinetics in these systems are primarily governed by the composition and physicochemical properties of the implant material, along with its interaction with the surrounding physiological environment. Passive systems can be further classified into solid implants and injectable depot formulations.

A. Solid Implants

Solid implants are monolithic, pre-fabricated devices with a predetermined geometry and drug load, typically administered via surgical implantation.

They can be non- biodegradable or biodegradable solid implants

B. Injectable Depot Systems:

Injectable depots are designed for minimally invasive administration and form a drug depot in situ after injection.

Now they can be microparticle implants or insitu forming implants ;

Microparticle Implants: These systems consist of polymer-based microparticles (1–1000 µm) loaded with drug, suspended in an injectable vehicle. Upon administration, the microparticles aggregate and release the drug via a combination of diffusion, polymer swelling, and degradation. Controlled manufacturing techniques such as emulsion-solvent evaporation allow precise tailoring of particle size and drug content.

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A prominent example is Lupron Depot®.

In Situ Forming Implants (ISFIs): These advanced systems involve injectable liquid formulations that solidify post-administration due to phase transitions. One common mechanism is solvent exchange-induced precipitation, wherein a biodegradable polymer (e.g., PLGA) and drug are dissolved in a biocompatible solvent like N-methyl-2-pyrrolidone (NMP). Upon injection, rapid diffusion of the solvent into bodily fluids causes the polymer to precipitate, forming a solid drug-releasing implant (e.g., Atridox®, Eligard®). Alternative mechanisms include thermally induced gelation using temperature-sensitive polymers (e.g., poloxamers) and in situ chemical cross-linking of injectable polymer precursors.

2. Active Infusion Devices (Implantable Pumps)

Unlike passive systems, active infusion devices are electromechanical systems capable of delivering drugs at highly programmable rates. These devices represent the pinnacle of precision and customization in drug delivery.

Mechanism and Design: Typically encased in a hermetically sealed titanium shell, an implantable pump contains a drug reservoir, power source (usually a battery), microprocessor-based electronic control unit, and a pumping mechanism. Drug delivery is achieved through a catheter that directs the drug to a targeted anatomical site, such as the intrathecal space or hepatic artery.

These biodegradable polymeric implants also broadly categorized into two main types based on their structural configuration and mechanism of drug release: reservoir-type and matrix-type devices. In reservoir-type implants, the active pharmaceutical ingredient is confined within a central core surrounded by a biodegradable polymer membrane that governs the rate of drug diffusion. This design enables relatively constant, zero-order release kinetics, making it suitable for clinical situations where steady plasma concentrations are critical. In contrast, matrix-type implants involve the uniform dispersion or dissolution of the drug throughout the polymer matrix. Drug release from these systems occurs via a combination of diffusion and polymer degradation, typically resulting in a biphasic release profile characterized by an initial burst followed by a slower, sustained release phase. The degradation rate of the polymer, drug loading, and matrix composition significantly influence the release behavior. Commonly employed biodegradable polymers include polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA), all of which degrade into metabolizable and non-toxic byproducts. The selection between reservoir and matrix systems is dictated by the therapeutic objectives, physicochemical characteristics of the drug, and desired release profile. This classification framework not only informs implant design but also facilitates the development of personalized and disease-specific treatment strategies.

Stages of Biodegradable Polymeric Implant Degradation and Clinical Implication :

Biodegradable polymeric implants undergo a sequence of physicochemical and biological transformations, ultimately resulting in the controlled release and complete elimination of the therapeutic agent and polymer matrix. The degradation process initiates with polymer hydration, where water molecules penetrate the polymer network, disrupting both primary and secondary structural interactions, including hydrogen bonding and van der Waals forces. This is followed by a progressive loss of mechanical strength, primarily attributed to the hydrolytic cleavage of ester bonds within the polymer backbone. As the polymer chains fragment, the matrix integrity diminishes, resulting in the loss of mass and the initiation of absorption of lower molecular weight fragments by surrounding tissues or through phagocytosis. Ultimately, these fragments undergo complete dissolution, yielding biocompatible and metabolizable byproducts such as glycolic acid and lactic acid, which enter natural metabolic pathways like the citric acid cycle.

An exemplary application of this technology is Zoladex®, a commercially available PLA/PLGA-based biodegradable implant designed for the sustained delivery of goserelin, a gonadotropin-releasing hormone (GnRH) agonist analog. Upon administration, goserelin exhibits an initial agonistic phase, stimulating gonadotropin release, which is subsequently followed by downregulation of GnRH receptors and suppression of gonadotropin secretion due to receptor desensitization. This biphasic response underlies the therapeutic efficacy of goserelin implants in conditions like endometriosis and sex hormone-dependent tumors (e.g., prostate and breast cancer), where hormonal suppression is clinically beneficial.

3D Printing for Implantable Drug Delivery: A Novel Approach to Thermolabile and High-Load Formulations :

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3D printing has emerged as a transformative technology in the design and fabrication of implantable drug delivery systems, offering unprecedented flexibility, precision, and personalization in pharmaceutical manufacturing. Unlike conventional implant fabrication methods that often rely on molding or extrusion at high temperatures, 3D printing enables the layer-by-layer construction of complex geometries and controlled drug-release profiles tailored to individual patient needs. A notable advancement in this field is the room-temperature 3D printing of drug-loaded implants, which presents a significant advantage for thermolabile drugs, peptides, and proteins that degrade under high thermal conditions. Traditional hot-melt extrusion (HME)-based 3D printing, as used for olanzapine (OLZ) orodispersible films (Cho et al., 2020), required high processing temperatures (160–170 °C) and achieved limited drug loading (5% w/w). In contrast, the novel room-temperature technique allows for the successful fabrication of OLZ-loaded implants with considerably higher drug content, without compromising the integrity of heat-sensitive compounds. Attempts to utilize modified HME at reduced temperatures (60–80 °C) revealed technical limitations, including poor extrusion at 60 °C and insufficient interlayer adhesion at 80 °C, underscoring the limitations of semi-thermal methods. Surface morphology analysis via scanning electron microscopy (SEM) confirmed the uniform dispersion of OLZ crystals within the implant matrix, with plate-like, square-shaped crystals indicative of crystalline form I, although full polymorphic identification would require further confirmation using X-ray diffraction (XRD). Notably, blank implants exhibited smaller PEO crystals, and no visible OLZ aggregation was detected, suggesting efficient distribution. Earlier reports by de Almeida et al. (2021) demonstrated PCL-based OLZ implants via HME but with lower drug loading (23% w/w), while similar implant systems have been explored for drugs like levothyroxine and islatravir (Barrett et al., 2018; Stewart et al.). The method presented here thus represents a promising step forward in the production of customizable, thermally stable, and high drug-load implants using 3D printing, potentially revolutionizing long-term drug delivery strategies in clinical settings.

Integration of Smart Implantable Drug Delivery Systems with Biosensors: A Convergence of Biotechnology, Microelectronics, and Personalized Medicine :

The fusion of biotechnology, microelectronics, and advanced materials science is catalyzing a transformative shift in therapeutic strategies, particularly through the development of smart implantable drug delivery systems (IDDS). These next-generation therapeutic platforms are designed not only for localized, sustained drug release but also for dynamic, real-time modulation of therapy based on a patient's immediate physiological status.

This shift marks the emergence of a "sense-and-treat" paradigm, wherein treatment regimens are autonomously and continuously tailored to the patient's biochemical milieu, heralding a new era of precision and personalized medicine.

Technical Convergence: Architecture and Functional Components:

Traditional drug delivery modalities, particularly those relying on systemic administration and fixed-dose schedules, are frequently hindered by challenges such as fluctuating drug plasma levels, poor patient adherence, and off-target toxicities. Implantable drug delivery systems were initially conceptualized to mitigate these issues by offering sustained, localized delivery of therapeutic agents. However, recent innovations are pushing the boundaries of these devices by integrating them with biosensing and real-time control capabilities.

The architecture of a smart IDDS typically incorporates three primary modules:

1. Drug Delivery Unit:

This module consists of a biocompatible polymeric reservoir or matrix, which encapsulates the active pharmaceutical ingredient (API). Drug release may be governed by passive mechanisms such as diffusion or degradation, or active mechanisms including microelectromechanical systems (MEMS), piezoelectric pumps, electrothermal actuators, or stimuli-responsive hydrogels that react to environmental triggers (e.g., pH, temperature, or electric fields).

2. Biosensor Interface:

Integrated biosensors form the sensing core of the system. These miniaturized analytical devices are capable of detecting specific physiological biomarkers such as glucose, lactate, interleukins, tumor necrosis factor-alpha (TNF-α),

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or local pH levels. Electrochemical biosensors, utilizing enzyme-based electrodes, field-effect transistors, or impedance spectroscopy, are widely employed due to their high sensitivity, rapid response, and ease of integration with implantable systems. The selection of biomarkers is disease-specific and crucial for ensuring accurate physiological monitoring.

3. Real-Time Monitoring and Control Module:

The real-time feedback mechanism is enabled through an onboard microprocessor or application-specific integrated circuit (ASIC). This control unit analyzes biosensor signals, interprets physiological trends, and triggers drug release based on pre-programmed therapeutic algorithms. This closed-loop feedback system facilitates precise dose titration in response to fluctuating patient needs, reducing the risk of overdose or under-treatment. Advanced systems may further incorporate wireless telemetry (Bluetooth Low Energy or RFID) to transmit data to external devices, allowing remote monitoring and clinician-led therapy adjustments.

they also provide clinical approaches in personalized medicine like Smart IDDS platforms are gaining momentum in the management of chronic and complex conditions such as diabetes mellitus, cancer, cardiovascular diseases, and autoimmune disorders. For instance, in diabetes management, glucose-sensitive insulin delivery systems are being developed wherein insulin release is dynamically regulated by real-time glucose concentrations. Similarly, implantable chemotherapeutic depots integrated with inflammatory cytokine sensors are under exploration for targeted, adaptive cancer therapy.

These systems epitomize the principles of personalized medicine, offering patient-specific pharmacokinetic profiles based on real-time biological cues. Moreover, customizable 3D-printed implants, tailored to an individual's anatomy and therapeutic requirements, are increasingly being utilized to enhance device biocompatibility and treatment precision.

The above graph compares drug concentration over a 24-hour period across three systems: manual dosing, traditional implants, and biosensor-guided implants.

Manual Dosing shows a rapid decline in drug levels, reflecting quick metabolism and clearance, with notable variability. This can lead to periods of sub-therapeutic levels or toxicity due to infrequent and less responsive dosing.

Traditional Implants offer a more consistent release profile than manual dosing, but they cannot adapt to real-time physiological changes, potentially leading to under- or over-dosing under certain conditions.

Biosensor-Guided Implants, however, demonstrate superior control with more stable concentrations. Oscillations in the curve reflect real-time adjustments based on sensor feedback (e.g., increasing release during rising biomarker levels and reducing when normal).

II. CONCLUSION:

The evolution of implantable drug delivery systems, particularly those employing biodegradable polymers, represents a significant leap forward in addressing the limitations of conventional drug administration routes. These systems offer numerous advantages, including sustained and controlled drug release, improved patient compliance, and elimination of frequent dosing or surgical removal, making them ideal for chronic and long-term therapies. The ability to tailor polymer degradation rates, leverage advanced fabrication techniques like 3Dprinting, andintegrate biosensors has propelled the field toward personalized and precision medicine.

Biodegradable implants, through mechanisms like bulk and surface erosion, enable fine-tuned therapeutic delivery, while innovations such as in situ forming depots and microparticles expand the landscape of minimally invasive therapies. The incorporation of biosensors and real-time monitoring transforms these implants into smart therapeutic platforms capable of dynamic, patient-specific drug administration—ushering in a new era of responsive, adaptive, and data-driven healthcare.

As global health priorities shift towards managing non-communicable diseases, the integration of biotechnology, material science, and microelectronics in drug delivery systems stands to redefine treatment paradigms. Continued research and clinical translation of these systems will be critical in realizing their full potential in enhancing therapeutic outcomes, reducing systemic toxicity, and elevating the standard of care for diverse patient populations.

Acknowledgement :- I would like to express my sincere gratitude to Scientist Dr. Hemachandran Ravikumar, for his invaluable support, expert

insights, and continuous encouragement throughout the development of this work. His scientific guidance helped shape the direction of this article and enriched its quality significantly.

I also acknowledge the crucial role of Artificial Intelligence tools, which aided in problem-solving, data visualization, and simplifying complex scientific concepts during the writing and structuring of this article.

Lastly, I extend my appreciation to all the resources-both human and digital-that contributed to overcoming obstacles and turning this research vision into reality.

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