

SMART IMPLANTS WITH ON-DEMAND DRUG RELEASE: A REVIEW

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ABSTRACT

Smart implants with on-demand drug release represent an advanced class of implantable drug delivery systems designed to overcome the limitations associated with conventional implants. Traditional implantable systems generally provide continuous drug release at fixed rates and lack responsiveness to changes in physiological or pathological conditions, which may result in inadequate therapy or increased adverse effects. Smart implants are engineered to release therapeutic agents selectively in response to specific endogenous physiological signals or externally applied stimuli. These systems utilize stimuli-responsive polymers, hydrogels, biodegradable matrices, nanomaterials, and microelectronic components to achieve controlled and precise drug delivery. Endogenous triggers such as pH variation, enzymatic activity, glucose concentration, and inflammatory mediators, as well as exogenous stimuli including light, magnetic fields, ultrasound, and electrical signals, have been extensively investigated for regulating drug release. Smart implants have shown significant potential in cancer therapy, diabetes management, infection control, ocular drug delivery, neurological disorders, and chronic disease treatment. This review discusses the principles, mechanisms, materials, classification, fabrication techniques, therapeutic applications, advantages, limitations, and future perspectives of smart implants with on-demand drug release, highlighting their importance in the development of precision and personalized medicine.

KEYWORDS: Smart implants; On-demand drug delivery; Stimuli-responsive systems; Implantable drug delivery systems; Controlled release.

INTRODUCTION

Implantable drug delivery systems (IDDS) is a medical device that have gained considerable attention due to their ability to provide sustained therapeutic action, reduce dosing frequency, and improve patient compliance^{44,50]}. They are placed surgically via minor incision within body. Although conventional implants offer sustained drug release, they generally operate with predetermined release kinetics and cannot adapt to the dynamic nature of disease progression or patient-specific requirements. Such limitations may compromise therapeutic effectiveness or lead to undesirable side effects.

Smart implants are modern implantable drug delivery systems developed to provide adaptive and need-based therapeutic intervention. Conventional implantable formulations generally deliver drugs in a continuous and pre-determined manner, without considering variations in disease severity or patient-specific physiological conditions. Such rigid release profiles may lead to reduced therapeutic effectiveness or unnecessary exposure to drugs. Smart implants have been designed to overcome these drawbacks by enabling controlled drug release only in response to specific biological or externally applied signals.^[1]

The design of smart implants is based on the incorporation of drug reservoirs within materials capable of sensing and responding to changes in the surrounding environment. These materials include stimuli-responsive polymers, biodegradable matrices, hydrogels, nanostructured materials, and, in some systems, microelectronic components. Upon exposure to a defined trigger, the implant undergoes a controlled physicochemical change that initiates drug release. Internal physiological triggers such as alterations in pH, enzyme levels, glucose concentration, temperature, or inflammatory mediators are commonly utilized. In addition, external triggers such as light, magnetic fields, ultrasound, and electrical stimulation allow precise regulation of drug release by healthcare professionals.

The functional content of smart implants involves careful selection of biocompatible materials, optimization of responsiveness, and fabrication of devices capable of maintaining long-term stability within the body. Drug release from these systems may occur through mechanisms such as polymer swelling, erosion, cleavage of stimulus-sensitive bonds, or changes in membrane permeability. Advances in polymer science, nanotechnology, and microfabrication have significantly improved the accuracy and reliability of these systems.

Smart implants have demonstrated potential benefits in the management of chronic conditions, including cancer, diabetes, ocular disorders, infections, and neurological diseases.^[24] By offering site-specific, responsive, and patient-oriented therapy, smart implants represent an important step toward the development of precision and personalized drug delivery systems.

EVOLUTION OF IMPLANTABLE DRUG DELIVERY SYSTEMS

During the early 1990s (approximately 1992–1995), significant progress in implantable drug delivery technology was achieved with the introduction of biodegradable polymers such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA). These polymers enabled the design of implants that gradually degraded within the body, improving biocompatibility and removing the requirement for surgical retrieval after the drug had been completely released. Although these systems provided sustained and predictable drug release, their release profiles were generally fixed and could not adapt to changes in physiological conditions.

In the early 2000s (around 2000–2005), advances in materials science, nanotechnology, and microfabrication techniques facilitated the development of more sophisticated implantable drug delivery platforms. These innovations allowed better control over drug release kinetics and improved precision in therapeutic delivery.

By around 2010 (2010–2012), the incorporation of microelectronic components and programmable microchip technology enabled implantable devices to release drugs at pre-programmed intervals.^[7] This advancement marked a major step toward controlled and programmable therapeutic administration.

From 2020 onwards, research has increasingly focused on smart implantable systems incorporating stimuli-responsive polymers and biosensor technologies.^[1,48] These modern implants are capable of responding to physiological triggers such as pH variations, temperature changes, enzymatic activity, or glucose levels. Such systems can monitor biological signals in real time and release drugs accordingly, representing an important advancement toward personalized and precision medicine.

PRINCIPLES OF SMART IMPLANTS

The principles of smart implants are based on the integration of drug delivery functions with intelligent response mechanisms that enable precise, controlled, and need-based therapy. Unlike conventional implantable systems that release drugs continuously at fixed rates, smart implants are designed to sense changes in the surrounding biological environment or respond to externally applied triggers and release therapeutic agents only when required. This adaptive behaviour forms the core principle of smart implant technology.

A fundamental principle of smart implants is the presence of a drug reservoir coupled with a stimulus-responsive component. The responsive element may be a polymer, hydrogel, membrane, or electronic interface that undergoes a predictable physicochemical change upon exposure to a specific stimulus. These changes may include polymer swelling or shrinkage, degradation, pore formation, or alteration in permeability, leading to controlled drug release. Smart implants may respond to endogenous stimuli such as pH variations, enzymatic activity, glucose concentration, temperature, or inflammatory markers, as well as exogenous stimuli including light, magnetic fields, ultrasound, or electrical signals.

Another important principle is biocompatibility and stability. Materials used in smart implants must be non-toxic, non-immunogenic, and capable of maintaining functionality over extended periods within the body. Precision and reproducibility of drug release are also critical, ensuring consistent therapeutic outcomes. Additionally, advanced smart implants may incorporate biosensors, microchips, or feedback systems that enable real-time monitoring and closed-loop control of drug delivery.

Overall, the principles of smart implants focus on responsiveness, precision, safety, and patient-specific therapy, making them a promising platform for controlled and personalized drug delivery.

MECHANISMS OF ON-DEMAND DRUG RELEASE

1. Endogenous Stimuli-Responsive Systems

- a. pH-responsive systems exploit pH differences between healthy and diseased tissues, particularly in tumours and inflamed sites.^[20]

- b. Enzyme-responsive systems release drugs in response to enzymes produced during pathological conditions such as infections.
- c. Glucose-responsive systems have been extensively studied for insulin delivery in diabetes management.

2. Exogenous Stimuli-Responsive Systems

- a. Light-triggered systems provide spatial and temporal control over drug release.^[10]
- b. Magnetic-responsive systems enable non-invasive activation using external magnetic fields.
- c. Electrical and ultrasound-triggered systems offer precise modulation of drug release through external stimulation.

The general mechanism of drug release from smart implants is shown in Fig.1

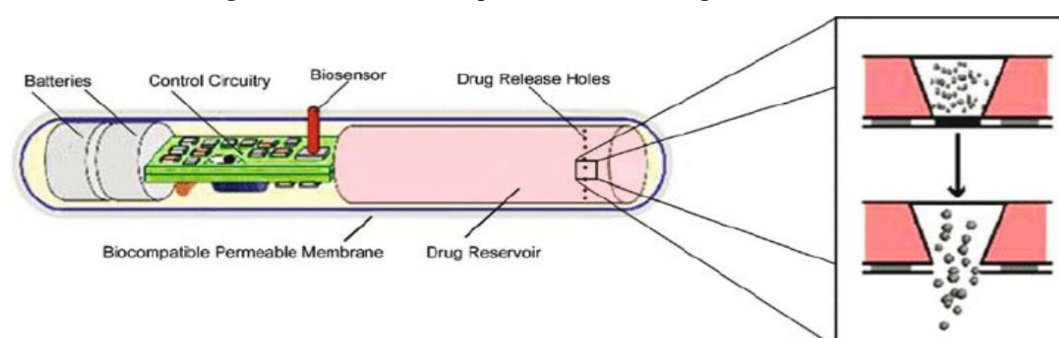


Figure 1: Schematic representation of a smart implant illustrating the drug reservoir, stimulus-responsive material, triggering stimulus, and controlled on-demand drug release.

THERMODYNAMIC AND KINETIC CONSIDERATIONS

Drug release is influenced by thermodynamic factors such as solubility and partitioning, kinetic factors including diffusion, erosion, and degradation.^[17] Mathematical modelling assists in predicting release behaviour and optimizing implant design.

MATERIALS USED IN SMART IMPLANTS

Smart implants employ a wide range of biocompatible materials, including stimuli-responsive polymers, biodegradable polymers, hydrogels, nanogels and conductive materials.^[9,20] Polymers such as chitosan and PNIPAM exhibit responsiveness to pH and temperature changes, while biodegradable polymers like PLGA and PLA support sustained release and eventual degradation. Hydrogels and nanogels are particularly attractive due to their high water content and tunable properties.

CLASSIFICATION OF SMART IMPLANTS

Smart implants can be classified based on the type of stimulus controlling drug release, including pH-responsive, enzyme-responsive, electro-responsive, magnetic-responsive, and photo-responsive systems.

Table 1: Different types of smart implants.

Type of smart implant	Triggering stimulus	Mechanism of drug release	Major applications
pH -responsive implants	pH change	Polymer swelling/degradation	Cancer, inflammation
Enzyme-responsive implants	Enzymatic activity	Enzymatic cleavage	Infection control
Glucose-responsive implants	Glucose levels	Affinity/enzymatic response	Diabetes
Magnetic-responsive implants	Magnetic field	Heat or movement	Targeted chemotherapy
Photo-responsive implants	Light	Photo-cleavage	Precision therapy
Electro-responsive implants	Electrical signal	Conductivity change	Neurological disorders

BIOCOMPATABILITY AND HOST RESPONSE

Biocompatibility is a fundamental requirement for smart implantable drug delivery systems, as these devices remain in direct contact with biological tissues for extended periods. Upon implantation, the material surface immediately interacts with blood proteins, leading to protein adsorption and activation of inflammatory pathways. This early phase is followed by recruitment of immune cells such as neutrophils and macrophages. If the material is not adequately compatible, persistent inflammation may occur, resulting in a foreign body reaction characterized by macrophage fusion and fibrous capsule formation around the implant. The development of a dense fibrotic layer can hinder drug diffusion, alter release kinetics, and reduce therapeutic efficiency. Therefore, careful selection of non-toxic, non-immunogenic, and biodegradable materials is essential. Surface modification strategies, including hydrophilic coatings, polyethylene glycol grafting, and zwitterionic functionalization, are commonly employed to minimize protein adsorption and cellular adhesion. In addition, controlling implant geometry, surface roughness, and degradation rate further influences host response. Long-term biocompatibility studies, including cytotoxicity, hemocompatibility, and chronic implantation evaluations, are critical to ensure safety and sustained performance. Optimizing the interaction between implant materials and host tissues ultimately enhances therapeutic reliability and clinical acceptance.^[18]

FABRICATION TECHNIQUES

Various fabrication methods have been employed in the development of smart implants, such as solvent casting, hot-melt extrusion, microfabrication techniques, and three-dimensional printing. Recent advances in 3D printing have enabled the production of patient-specific implants with precise drug loading and release characteristics. The development of implantable and smart drug delivery systems requires precise fabrication methods to ensure controlled drug loading, predictable release profiles, and structural stability of the implant. Various fabrication techniques have been explored in pharmaceutical and biomedical engineering to design implants with desired therapeutic performance. The choice of fabrication method depends on several factors including the type of polymer used, drug properties, implant geometry, and the required drug release pattern. Commonly employed fabrication techniques include solvent casting, hot-melt extrusion, microfabrication technologies, and three-dimensional (3D) printing.^[44]

1. Solvent Casting

Solvent casting is one of the most widely used and straightforward techniques for the preparation of polymeric implants and drug delivery films. In this method, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, ethanol, or acetone. The drug is then dispersed or dissolved in the polymeric solution to form a homogeneous mixture. This mixture is poured into molds or flat surfaces and allowed to dry under controlled conditions so that the solvent gradually evaporates, leaving behind a solid polymeric matrix containing the drug.

This technique is commonly used for preparing biodegradable implants using polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL). The major advantages of solvent casting include its simplicity, low cost, and minimal equipment requirements. It also allows relatively uniform drug distribution within the polymer matrix. However, the presence of residual organic solvents can be a concern, especially for sensitive drugs or biomedical applications. Additionally, incomplete solvent removal may affect the safety and mechanical strength of the implant.^[43]

2. Hot-Melt Extrusion

Hot-melt extrusion (HME) is another important fabrication technique used in the development of implantable drug delivery systems. In this process, the drug and polymer are mixed and heated above the melting temperature of the polymer. The molten mixture is then forced through an extruder barrel and shaped through a die to form implants of desired geometry such as rods, films, or cylindrical devices.

One of the main advantages of hot-melt extrusion is that it is a solvent-free process, which eliminates issues related to residual solvents. It also allows continuous manufacturing and improved control over implant shape and drug distribution. This technique is particularly suitable for thermoplastic polymers used in controlled drug delivery systems. However, the major limitation of hot-melt extrusion is the exposure of the drug to high temperatures, which may cause degradation of heat-sensitive drugs such as proteins or certain small-molecule drugs.

3. Microfabrication Techniques (MEMS)

Microfabrication techniques, commonly used in microelectromechanical systems (MEMS), have significantly contributed to the development of advanced implantable drug delivery devices. These techniques involve the use of microengineering processes such as photolithography, etching, and thin-film deposition to fabricate extremely small structures and devices with high precision.

Microfabricated implants can incorporate multiple drug reservoirs, microchannels, and valves that allow controlled or programmable drug release. These systems are particularly useful for developing microchip-based implantable drug delivery devices capable of delivering drugs at predetermined intervals. The high precision of microfabrication techniques enables accurate dosing and spatial control of drug release.^[11] However, these systems require sophisticated equipment and clean-room facilities, which increases the cost and complexity of manufacturing.

4. Three-Dimensional (3D) Printing

Three-dimensional printing, also known as additive manufacturing, has recently emerged as a promising fabrication technique for personalized implantable drug delivery systems. In this method, implants are constructed layer by layer using computer-aided design (CAD) models. Various 3D printing technologies such as fused deposition modeling (FDM), stereolithography (SLA), and selective laser sintering (SLS) can be used depending on the material and application.

3D printing offers several advantages in pharmaceutical implant fabrication. It allows the production of implants with complex geometries, precise drug loading, and customized dimensions tailored to individual patient needs. Additionally, drug release profiles can be modified by altering the internal structure, porosity, or composition of the printed implant. Despite these advantages, challenges such as high equipment cost, material limitations, and regulatory considerations still need to be addressed before widespread clinical implementation.

Table 2: Types of fabrication techniques.

Technique	Principle	Advantage	Limitation
Solvent casting	Polymer dissolution & drying	Simple, economical	Residual solvent
Hot-melt extrusion	Heat-based shaping	Solvent-free	Not for heat-sensitive drugs
Microfabrication (MEMS)	Micro-scale device fabrication	High precision	Expensive
3D printing	Layer-by-layer fabrication	Personalized implants	High equipment cost

THERAPEUTIC APPLICATIONS

Smart implants have demonstrated promising applications in several therapeutic areas. In cancer therapy, localized drug release minimizes systemic toxicity. In diabetes management, glucose-responsive implants provide controlled insulin delivery. Ocular drug delivery systems improve drug bioavailability and reduce dosing frequency. Additionally, smart implants play an important role in infection control, chronic pain management, and neurological disorders.

Table 3: Various applications of smart implants.

Disease condition	Drug	Type of smart implant	Therapeutic benefit
Cancer	Doxorubicin	pH-responsive implant	Reduced toxicity
Diabetes	Insulin	Glucose-responsive implants	Controlled glycemia
Glaucoma	Timolol	Ocular smart implant	Improved bioavailability
Infection	Antibiotics	Enzyme-responsive implant	Localized therapy
Chronic pain	Analgesics	Electro-responsive implant	On-demand relief

STERILIZATION AND STABILITY

Sterilization is a critical step in the development of smart implantable drug delivery systems, as these devices are introduced directly into sterile body environments. The selected sterilization method must effectively eliminate microbial contamination without compromising the structural integrity, drug stability, or stimulus-responsiveness of the implant. Conventional techniques such as steam sterilization are often unsuitable because elevated temperature and moisture may degrade polymers, alter drug crystallinity, or disrupt sensitive electronic components. Alternative approaches including gamma irradiation, electron beam irradiation, and ethylene oxide treatment are more commonly employed. However, ionizing radiation can induce polymer chain scission or crosslinking, thereby modifying mechanical strength and release kinetics. Ethylene oxide, while effective at low temperatures, requires careful removal of residual gas to prevent toxicity.

Stability considerations extend beyond sterilization and include long-term physicochemical integrity during storage and after implantation. Factors such as moisture uptake, oxidative degradation, hydrolysis of biodegradable polymers, and premature drug diffusion may affect therapeutic performance. For stimuli-responsive implants, maintaining sensitivity to environmental triggers over time is particularly important. Accelerated stability studies under controlled temperature and humidity conditions are conducted to predict shelf life and ensure consistent drug release behavior. Proper packaging, desiccants, and protective coatings are often utilized to enhance storage stability. Comprehensive evaluation of sterilization compatibility and long-term stability is essential to ensure safety, efficacy, and regulatory compliance of smart implant systems.

REGULATORY CONSIDERATIONS

Regulatory approval of smart implantable drug delivery systems is complex because these products often combine characteristics of medical devices, pharmaceutical formulations, and, in some cases, electronic components. As combination products, they must satisfy requirements related to safety, efficacy, quality, and performance under both drug and device regulatory frameworks. Preclinical evaluation typically includes biocompatibility testing, mechanical integrity assessment, sterility validation, degradation studies, and in vitro–in vivo correlation of drug release behavior. Long-term implantation studies in suitable animal models are necessary to assess chronic toxicity, inflammatory response, and functional reliability.

ADVANTAGES

Smart implants offer precise and controlled drug delivery by releasing therapeutic agents only when required, thereby minimizing systemic side effects and drug wastage. Their ability to respond to physiological or external stimuli enables site-specific and patient-tailored therapy, improving therapeutic efficacy. Smart implants reduce dosing frequency and enhance patient compliance, particularly in chronic disease management. Additionally, they maintain consistent drug levels, allow on-demand dosing, and may incorporate feedback mechanisms for real-time monitoring, making them a promising approach in controlled and personalized drug delivery.

LIMITATIONS AND CHALLENGES

Despite their therapeutic advantages, smart implants face several limitations that hinder widespread clinical adoption. The design and fabrication of smart implants are complex and often involve advanced materials, microelectronics, or nanotechnology, leading to high development and manufacturing costs. Long-term biocompatibility remains a concern, as prolonged implantation may trigger inflammatory responses or fibrous tissue formation that can affect device performance. Maintaining stability and consistent responsiveness of stimuli-sensitive materials over extended periods is challenging. Additionally, sterilization processes may alter material properties and reduce functionality. Regulatory approval for smart implants is stringent due to safety and performance requirements, further delaying clinical translation and commercialization.

MARKETED SMART IMPLANTS

Here are smart drug delivery systems with their brand names and drugs.

Table 4: Marketed Implantable Drug Delivery Systems (Smart / Controlled Implants).

Brand Name	Drug	Application	Company	Year Approved
Implanon® / Nexplanon®	Etonogestrel	Hormonal contraceptive implant	Merck	2006 / 2011
Probuphine®	Buprenorphine	Opioid dependence treatment	Titan Pharmaceuticals	2016
Ozurdex®	Dexamethasone	Retinal diseases (macular edema)	Allergan	2009
Retisert®	Fluocinolone acetonide	Chronic non-infectious uveitis	Bausch & Lomb	2005
Iluvien®	Fluocinolone acetonide	Diabetic macular edema	Alimera Sciences	2014
Durysta®	Bimatoprost	Glaucoma treatment	Allergan	2020

FUTURE PERSPECTIVES

Future developments in smart implants are expected to focus on multifunctional and fully autonomous systems capable of real-time sensing and feedback-controlled drug release. Advances in biodegradable electronics, wireless communication, and artificial intelligence may enable closed-loop implants that deliver patient-specific therapy with high precision. Improved biocompatible materials and minimally invasive implantation techniques are also anticipated to enhance safety, acceptance, and long-term clinical application of smart implants in personalized medicine.

CONCLUSION

Smart implants represent a significant advancement in implantable drug delivery by enabling precise, responsive, and patient-specific therapy. Their ability to release drugs on demand in response to physiological or external stimuli helps overcome the limitations of conventional implant systems, including fixed dosing and systemic side effects. By

integrating stimuli-responsive materials, biodegradable polymers, and advanced control mechanisms, smart implants improve therapeutic efficacy and patient compliance. Although challenges related to cost, long-term safety, and regulatory approval remain, continued progress in materials science and biomedical engineering is expected to support their broader clinical translation and role in personalized medicine.

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