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Review

Rise of implantable drugs: A chronicle of breakthroughs in drug delivery systems

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ABSTRACT

In recent years, implantable drug delivery systems (IDDSs) have undergone significant advancements because they offer many advantages to patients and health care professionals. Miniaturization has reduced the size of these devices, making them less invasive and easier to implant. Remote control provides more precise medication delivery and dosage. Biodegradable implants are an additional advancement in implantable drug delivery systems that eliminate the need for surgical removal. Smart implants can monitor a patient's condition and adjust their drug doses. Long-acting implants also provide sustained drug delivery for months or even years, eliminating the need for regular medication dosing, and wireless power and data transmission technology enables the use of devices that are more comfortable and less invasive. These innovations have enhanced patient outcomes by enabling more precise administration, sustained drug delivery, and improved health care monitoring. With continued research and development, it is anticipated that IDDSs will become more effective and provide patients with improved health outcomes. This review categorizes and discusses the benefits and limitations of recent novel IDDSs for their potential therapeutic use.

1. Introduction

An implantable drug delivery system (IDDS) is a surgically implanted medical device designed to deliver medication or therapeutic agents directly to targeted tissues or organs within the body, enabling localized and controlled drug administration. These devices are typically small, programmable pumps or reservoirs that are implanted beneath the skin and coupled to a catheter or other pharmaceutical delivery system (Fayzullin et al., 2021). Many medications, including analgesics (Airemwen et al., 2021), antibiotics (Cui et al., 2021), chemotherapeutic treatments (Wang et al., 2020), and insulin (Kim et al., 2020), can be delivered through IDDSs. The widespread acceptance of this delivery system could be because the benefits of IDDSs, such as precise distribution of the drug to the target tissue to avoid bioavailability or first-pass metabolism concerns, enable the reduction the active dose. Adverse effects can be minimized by lowering systemic concentrations of the active substance and eliminating the risk of improper drug administration. Lastly, these systems can prolong and regulate a drug's dosage, rendering the treatment independent of patient compliance.

As shown in Fig. 1, IDDSs were first used in the 1930 s when hormone-containing pellets were subcutaneously implanted in cattle and poultry (Kleiner and Wright 2013). The first clinical use of IDDSs for hormonal therapy in women was reported by Bishop in the 1960 s (Santos et al., 2014). A few more implantable drug formulations were briefly studied at this time. During the 1970 s and 1980 s, the first fully implantable infusion pump was invented by Robert Fischell (Buchwald et al., 1985) and became the first implantable infusion pump for insulin delivery approved by the US Food and Drug Administration (FDA). Moreover, the Norplant contraceptive device was also developed during this period (Peralta et al., 1995). In the 1990 s, new technological

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advancements in IDDSs were implemented in an effort to improve drug administration convenience, efficacy, and patient compliance. Advancements in microfabrication techniques and incorporation of microelectronics made it possible for devices to be significantly smaller and more precise (Ainslie and Desai 2008). Additionally, the use of biodegradable materials, such as poly(lactide–co-glycolide) (PLGA) (Fung 1996), poly[bis(p-carboxyphenoxy) propane-co-sebacic acid] (Duangjit 2016), and polycaprolactone (Darney et al., 1989), for implantation increased, eliminating the need for surgical removal of the device once the drug was depleted. During the 2000 s, research and development focused on biocompatibility and precision drug delivery, eventually enabling controlled release of drugs over extended periods. For example, the Duros® (ALZA Corporation, California, USA) subcutaneous implantable drug delivery osmotic pump platform is intended to deliver a continuous stable dose and accurate drug release for $\leq$ 12 months, making it suitable for a narrow range of therapeutic drugs (Stevenson et al., 2000). In the 2010 s, electronics and wireless control technologies were introduced in IDDSs (Koo et al., 2020). Choi and coworkers developed bioresorbable electronic systems encapsulated in polyanhydride-based polymers, which offer a promising, non-toxic solution for temporary implants that degrade safely in the body, thereby eradicating the need for secondary surgery (Choi et al., 2020). From 2011 to 2020, IDDSs tended to become more individualized, and smart drug delivery systems were implemented to respond to the changing requirements of the body and adjust drug delivery accordingly (Mazidi et al., 2022).

This review aims to comprehensively examine the advancements, benefits, and limitations of IDDSs with a focus on their design, materials, and clinical applications. The primary objective is to provide an in-depth analysis of the current state of IDDS technology, highlighting recent innovations such as biodegradable materials, microchip-based systems, and wireless control mechanisms. By evaluating the therapeutic potential and challenges associated with these systems, this review seeks to offer insights into how IDDSs can be further optimized to improve patient outcomes and address existing barriers in drug delivery. Additionally, the review will explore future directions and emerging trends that could shape the next generation of implantable drug delivery technologies.

2. Advantages and limitations

Implantable dosage forms offer a number of advantages for drug delivery systems. For example, continuous drug delivery is possible with IDDSs, which might be advantageous for patients who require long-term treatment or have trouble adhering to medication schedules. These technologies permit the precise control of drug release, which can prevent adverse effects and maximize pharmacological therapy (Park 2014). Technologies within IDDSs that enable precise control of drug release include microchip-based systems, which offer programmable drug release (Sutradhar and Sumi 2016, Homewood and Heyer 2017), and osmotic pumps, which provide a constant drug delivery rate (Almoshari 2022). By decreasing medication exposure to non-targeted tissues, focused drug delivery to certain tissues or organs can help prevent side effects (Rosengart et al., 2005, Barik and Chakravorty, 2019). IDDSs can enhance medication adherence by eliminating the requirement for daily or frequent dosing, thereby minimizing missed doses (Santos et al., 2014). An IDDS can provide long-term therapy without repeated implantation, which can be very beneficial for patients with chronic diseases (Chandrashekar and Udupa 1996). Compared with conventional drug delivery methods, IDDSs can lower the dosing frequency, which can increase patient convenience and compliance (Kuno and Fujii 2011). Lastly, IDDSs developed with telemedicine, which utilizes technology to provide remote medical care and manage patient treatments, allowing healthcare providers to monitor and adjust therapies without in-person visits, can be further enhanced by incorporating artificial intelligence (AI) and machine-learning algorithms. These advancements enable physicians to remotely adjust the rate of drug release from implantable devices, thereby optimizing therapeutic efficacy (Ross et al., 2017).

In addition to their numerous benefits, IDDSs must also overcome certain disadvantages. For example, surgical insertion is required for an IDDS, which can raise the risk of infection or tissue injury (Graham 1978). The invasive nature of these devices can cause patient discomfort and requires skilled medical professionals for proper placement and maintenance. An IDDS may malfunction or fail, resulting in insufficient drug delivery or burst release and dose dumping, which reduces the drug's bioavailability, and may then require additional surgery. Therefore, before implanting a device, its accuracy of dose release and reliability also need to be validated (Chavda et al., 2022). Another limitation is the restricted drug loading capacity of IDDSs, which can limit the types of drugs that can be administered by these systems (Kumar and Pillai 2018). IDDSs may be prohibitively expensive for some patients, limiting its accessibility (Long et al., 2013). IDDSs may have restricted options for certain types of drugs, such as those that are insoluble, chemically unstable or easily degraded, have high molecular weights, or are highly reactive or toxic (Kumar and Pillai 2018). Lastly,

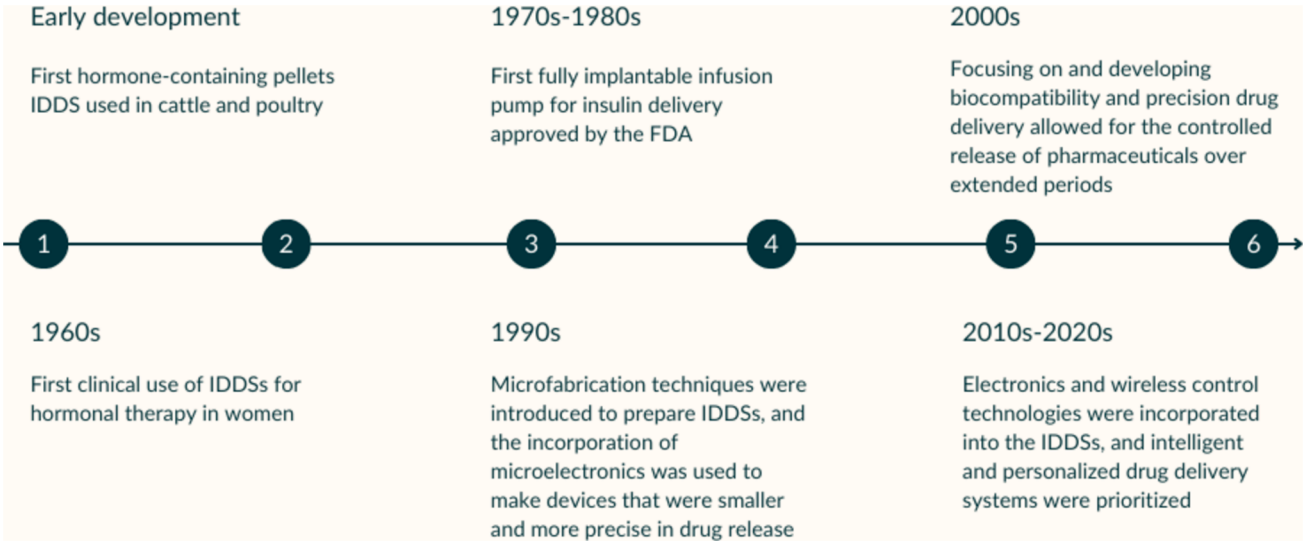

Fig. 1. Evolutionary timeline of implantable and insertable drug delivery systems.

IDDSs necessitate routine monitoring and upkeep to guarantee appropriate performance and prevent problems (Kar et al., 2022). Due to several limitations of conventional IDDSs, numerous research and innovations have been developed to address these issues, as discussed in this review.

3. Materials used in implantable drug delivery systems

IDDSs can be made from various materials, depending on their intended use and type of drug. Typically, IDDSs are made of biocompatible materials, meaning they are well-tolerated by the body and do not provoke an immune response or rejection. Materials for IDDSs have been categorized into five major groups: polymers, metals, ceramics, composites, and hydrogels.

3.1. Polymers

For the preparation of IDDSs, both biodegradable and non-biodegradable polymers have been used (Stewart et al., 2018). Nevertheless, non-biodegradable polymers are less popular since surgical removal is necessary or they accumulate in the body after use (Dash and Cudworth II, 1998). Therefore, biodegradable polymers, such as poly (lactic acid) (PLA) (Vlachopoulos et al., 2022), poly(glycolic acid) (PGA) (Brannon-Peppas and Vert 2000), PLGA (Sequeira et al., 2018), and poly (fatty acid dimer-co-sebacic acid) (Domb and Kubek 2001), are commonly used in IDDSs due to their biocompatibility, mechanical strength, flexibility, and ease of manufacturing (Anderson and Shive 1997).

3.2. Metals

Metals, such as titanium (Ma et al., 2021) and stainless steel (Barber et al., 2021), are often used in implantable devices due to their strength, biocompatibility, and resistance to corrosion. Titanium has always been regarded as one of the gold standard materials for orthopedic implants, but these implants can still present challenges, such as pain, bacterial infections, insufficient osseointegration, immune rejection, and difficulty in personalizing treatment in the clinic (Pavithra and Doble 2008). Therefore, titanium implants loaded with drugs for local administration have gradually attracted the attention of many researchers because they can effectively reduce inflammation levels, lower the endophytic bacterial infection risk, and regulate bone tumor-cell progression by maintaining the balance of bone metabolism around the titanium implants (Maher et al., 2018). Moreover, various types of drugs have been added to titanium implants to enhance antibacterial (Fathi et al., 2019), antitumor (Maher et al., 2017), and osseointegration effects (He et al., 2020).

3.3. Ceramics

Bioceramics, such as silica-based ordered mesoporous materials, are used in implantable devices for bone regeneration applications due to their high biocompatibility, bioactive behavior, high drug-loading capacity, and resistance to corrosion (Colilla et al., 2008). Recent chemical and technological advancements on the nanometer scale have enabled fabrication of mesoporous silica materials with specific structural and textural features to achieve more control over molecular loading and release kinetics. In addition, organic alteration of mesoporous silica walls has been identified as a crucial method for modulating molecule adsorption and delivery rates (Vallet-Regí, 2010).

3.4. Composites

Composites made from combinations of materials can offer new unique properties or improve current ones, such as high strength, biocompatibility, and controlled drug release. There are numerous reports of using polymer composites or blends for achieving different goals. For example, several research studies have used a composite material between ceramic and biodegradable polymers, such as gelatin and collagen, as the drug carriers, in which release patterns and mechanical properties strongly depended on the crosslinking level of gelatin/collagen (Shibata et al., 2005, Takahashi et al., 2005, Habraken et al., 2007). Polylactide-co-glycolide and hydroxyapatite have also been used in a bone-repair implant, and the product has been tested in swine mandibular defects (Stevanovic et al., 2022).

3.5. Hydrogels

Hydrogels are water-absorbing polymer networks that can hold large amounts of drugs and release them slowly over time. This formulation can be used for transscleral drug delivery for retinoblastoma treatment, as shown by Ana-Irina Cocarta and colleagues (Cocarta et al., 2019). Their study used a novel hydrogel implant capable of delivering therapeutically effective doses of the hydrophilic low molecular weight anticancer drugs topotecan and vincristine. The proposed hydrogel implant is bi-layered, with an inner hydrophilic layer of 2-hydroxyethyl methacrylate serving as a reservoir for the chemotherapeutic agent and an outer hydrophobic layer of 2-ethoxyethyl methacrylate functioning as a barrier to protect the surrounding vascularized tissue from the cytotoxicity of the delivered chemotherapeutics (Cocarta et al., 2019).

4. Design of implantable drug delivery systems

Designing IDDSs requires careful consideration of several factors, including the type of medication delivered, the target site in the body, the desired duration of drug delivery, and the patient's individual needs and preferences. The key considerations in the design of IDDSs (Kumar and Pillai 2018) are shown in Fig. 2.

4.1. Material selection

The materials used to construct the implantable device must be biocompatible and able to withstand certain conditions in the body, such as high temperature and acidic environments. Common materials used for IDDSs include titanium, stainless steel, and biodegradable polymers as mentioned in the previous section. The metabolism and clearance of IDDSs are also critical factors to be concerned in the material selection step because it influence their safety, effectiveness, and long-term use. Implants are designed using materials that interact with the body's physiological environment, and their biocompatibility largely determines how they are metabolized and eventually cleared from the body. Biodegradable implants, often made from materials such as PLA, PGA, and PLGA, are metabolized through natural biochemical pathways. These polymers degrade into smaller monomers like lactic acid and glycolic acid, which are then absorbed by the body and eliminated via normal metabolic processes, such as the citric acid cycle. This gradual degradation process reduces the need for surgical removal, making biodegradable implants especially useful for temporary therapies (Prakasam et al., 2017). On the other hand, non-biodegradable implants, including those made from metals like titanium and stainless steel or ceramics, are designed to remain intact within the body for extended periods. Their clearance primarily depends on mechanical stability and the absence of immune response rather than metabolism. However, these implants may require removal if they cause complications, such as infections or mechanical failures, necessitating surgical intervention (Magill et al., 2023). The clearance of implantable materials also involves interactions with the immune system. For instance, biodegradable implants may provoke a mild inflammatory response as the body recognizes and breaks down foreign materials. In contrast, non-biodegradable implants must be coated with biocompatible materials to minimize immune reactions (Tillman 2021).

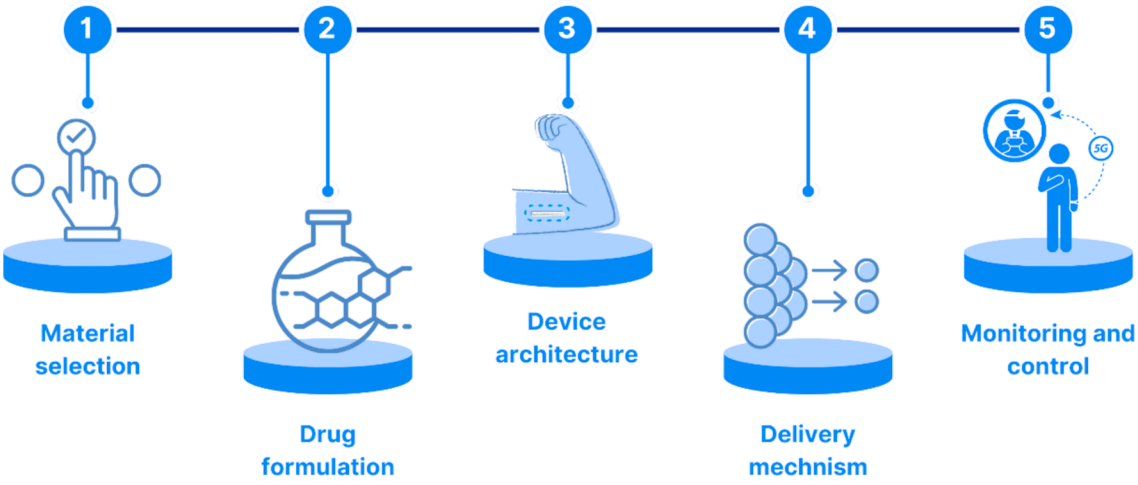

Fig. 2. Design process of implantable drug delivery systems.

4.2. Drug formulation

Drugs intended for delivery through IDDSs must be formulated to provide sustained or controlled release, ensuring consistent therapeutic levels over extended periods. These formulations often utilize specialized coatings, microspheres, or other advanced technologies to modulate release rates. Biodegradable polymers like PLA, PGA, and PLGA can be tailored to adjust degradation and drug release kinetics, enhancing formulation flexibility. The use of these materials allows the formulation of drugs that release slowly over time or respond to environmental triggers within the body.

4.3. Device architecture

The architecture of an implantable device is influenced by its target site and the desired duration of drug delivery. Devices can be designed as monolithic or reservoir-type systems, each offering distinct advantages. Monolithic systems have the drug uniformly dispersed within a polymer matrix, while reservoir systems contain a drug core enclosed by a permeable membrane, allowing for controlled release. Some IDDSs are refillable, enabling long-term drug delivery with minimal intervention.

4.4. Delivery mechanism

The method of drug delivery will depend on the specific requirements of the drug being delivered and the target site in the body. Drug release mechanisms from implantable systems are primarily classified into four types: matrix degradation, controlled swelling, osmotic pumping, and passive diffusion. In controlled swelling, drug release is regulated by solvent penetration into the device matrix, which leads to a slower release rate compared to diffusion, and matrix degradation can further enhance effectiveness. Osmotic pumping and passive diffusion are particularly effective for linear drug delivery, where the amount of released drug is proportional to the square root of the release time. Osmotic pumping utilizes osmotic pressure, driven by water absorption, to control the delivery rate, resulting in a constant release rate. Diffusion involves the spontaneous movement of molecules from one region to another, driven by a concentration gradient within a diffusional barrier. The release kinetics in systems using swelling, osmotic pressure, or passive diffusion are influenced by factors such as the solubility and diffusion coefficient of the drug in the polymer, the drug load, and the in vivo degradation rate of the polymer. These mechanisms are essential for achieving controlled and sustained drug release in implantable delivery systems (Stewart et al., 2018).

4.5. Monitoring and control

Advanced IDDSs may incorporate sensors and monitoring technologies to track drug release and ensure correct dosing. For example, recent case studies have demonstrated the use of microelectromechanical systems (MEMS) sensors in IDDSs to monitor drug release kinetics in real-time, enhancing treatment precision (Chircov and Grumezescu 2022). In a study by Lee et al. (2019), an implantable multireservoir device equipped with MEMS technology allowed for on-demand and pulsatile delivery of human growth hormone. The results showed that when implanted in living animals, the device could deliver the drug reproducibly by rupturing a stimulus-responsive membrane only when near-infrared irradiation was applied externally. This method enabled precise drug delivery without causing complications.

The design of IDDSs requires a multidisciplinary approach, involving expertise in materials science, drug formulation, biomedical engineering, and clinical medicine. With careful consideration of these factors, IDDSs can offer a safe, effective, and convenient drug deliver solutions for patients.

5. Implanted sites

The selection of the location for IDDSs is contingent upon a variety of factors, such as the pharmacological properties of the drug and the intended therapeutic outcome. Commonly used implantation sites include subcutaneous regions, the ocular area, neurological sites, and cardiovascular system. Determining the most appropriate implantation site depends highly on the specific factors involved, such as the specific pharmacological agent, projected therapeutic impact, and the individual patient's medical and personal needs.

5.1. Subcutaneous

The most prevalent type of implant site for IDDSs is subcutaneous. Typically, an IDDS is implanted in the abdomen or upper arm. These locations are comparatively accessible, and the implant is adequately protected from the elements. Hormones, such as etonogestrel (Implanon®) (Funk et al., 2005), or pain medications, such as bupivacaine (Exparel®) (Vyas et al., 2016), are frequently administered via subcutaneous implants. Commonly, the release of the implanted drug occurs over approximately 3–12 months. Subcutaneous implants provide many benefits, including long-lasting medication or health monitoring, convenience due to their small size and ease of insertion and removal, and efficacy of the delivered medication or monitoring of health directly beneath the skin. However, there are potential risks, such as possible

infection, discomfort during insertion, and the need for professional removal when the implant is no longer required (Rael et al., 2020).

5.2. Ocular

Recent ocular drug delivery systems, such as eye drops, while commonly used, have significant drawbacks. The major limitations of eye drops include poor bioavailability, as less than 5 % of the drug typically reaches the targeted ocular tissues due to barriers like tear dilution, rapid blinking, and drainage through the nasolacrimal duct. Additionally, frequent dosing is often required to maintain therapeutic drug levels, which can lead to patient non-compliance, especially in chronic conditions. Eye drops also provide limited control over drug release, resulting in fluctuating drug concentrations and suboptimal therapeutic effects. These drawbacks underscore the need for more advanced drug delivery systems, such as implants or inserts, which offer controlled, sustained drug release and improved patient outcomes in the treatment of chronic eye diseases. Ocular implants deliver medication directly to the eye, maintaining a stable eye environment, preventing or slowing the progression of eye diseases, or monitoring various eye health parameters to facilitate early disease diagnosis and management. They are frequently used to treat glaucoma and other eye conditions (Yadav et al., 2019). Ocular implants provide more effective and convenient alternatives to conventional treatments, such as eye drops and laser surgery, and deliver medication precisely where it is required, with less frequent application needed. However, they carry risks, including possible infection, insertion discomfort, and the need for surgical insertion by a medical professional (Dave 2016). Biodegradable implants for easier removal, targeted drug delivery (TDD) for increased efficacy (Lee et al., 2010), and AI-powered monitoring implants for real-time disease diagnosis and management are promising developments for the future of ocular implants (Bruen et al., 2017, Jin et al., 2023). Despite the inherent dangers, advancements in technology probably will make ocular implants more effective and secure for a variety of eye diseases.

5.3. Neurologic

Neurologic implants are medical devices that are inserted into the brain or nervous system to treat or manage a variety of medical conditions. They serve a variety of purposes, including drug delivery, nerve stimulation, and brain electrical activity recording. For drug delivery, neurologic implants were developed to overcome drug delivery challenges caused by the blood–brain barrier, which prevents most drugs from entering the target site in the brain (Zhao et al., 2023). Localized and site-specific drug delivery methods represent a significant advancement in treating brain diseases, offering a more effective and minimally invasive alternative to systemic drug administration. Practical application of this method hinges on the use of advanced technologies and miniaturized implants or devices that enable controlled drug delivery. Recent research has expanded the range of innovative neural implants and platforms available for such purposes. For example, Christopher et al. developed a ground-breaking brain implant that integrates a microfluidic ion pump with an electrocorticography device, enabling electrophoretic drug delivery on demand and simultaneous recording of local neural activity. This novel advancement in cortical drug delivery systems, demonstrated in a rodent model, presents a new method to treat neurological disorders by delivering drugs precisely when and where they are needed (Proctor et al., 2019).

5.4. Cardiovascular

Cardiovascular implants for drug delivery, such as stents (Tada et al., 2013, Jeger et al., 2020), grafts (Dahl et al., 2011), and patches (Mei and Cheng 2020), are drug-eluting medical devices within the cardiovascular system that administer medication directly to the afflicted area (Arora et al., 2019). Drug-eluting stents in the form of drug-coated metallic stents and biodegradable formats are commercially available (Livingston and Tan 2016). For example, Xience V® (Fig. 3a) is a metallic stent coated with everolimus for treating cardiovascular diseases, such as thrombosis and ischemia-driven target lesion revascularization (Gada et al., 2013, FDA 2021). Cardiac patches are implantable devices for repairing cardiomyocytes damaged by heart disease, such as coronary artery disease or myocardial infarction. Cardiac patches consisting of bioactive compounds, such as growth factors, extracellular vesicles, and microRNAs, and substrate scaffolds mimic the features of healthy native myocardium (Fig. 3b) (Mei and Cheng 2020). Vascular grafts are medical devices designed to replace or bypass damaged or diseased blood vessels within the human body that can be loaded with various kind of drugs. For example, Rossella Dorati and team developed vancomycin-loaded vascular grafts prepared by the electrospinning technique (Fig. 3c). They reported that the surfactant-mediated reduction of precipitates on fiber surfaces contributed to controlled release of vancomycin, extending up to 168 h, that surpassed the minimum inhibitory concentration, thereby potentially averting antibiotic resistance while effectively managing local drug release (Dorati et al., 2021).

However, these implants do carry risks, including of infection, potentially high costs, and the need for surgical insertion by a trained medical professional. Looking to the future, the field is evolving with new technologies in development, such as biodegradable implants, TDD, and AI-aided diagnostics and treatment plans, promising more effective and safer options. Overall, cardiovascular implants for drug delivery are a promising intervention for a variety of cardiovascular diseases, and their effectiveness and safety are likely to increase as the technology develops.

6. Recent advances

IDDSs have been intensively developed over the last two decades to extend and optimize their applications. Dosage form development has progressed in several directions, such as preparing from biodegradable materials, microchip-based implantable drugs, and using 3D printers to fabricate the dosage form. In this section, several advanced IDDSs from recent research articles are summarized and discussed.

6.1. Biodegradable implantable drug delivery systems

One of the major challenges of IDDSs is the type of implantable materials. In the past, only non-biodegradable materials were used for implantable devices; therefore, patients needed to have surgery twice (implantation and removal), which caused significant inconvenience (Aj et al., 2012). Therefore, biodegradable IDDSs were developed and have emerged as a promising technology to improve the efficacy and safety of conventional implantable drug therapies.

Typically, the systems contain biocompatible and biodegradable polymers implanted in the body to release drugs in a sustained controlled manner. The biodegradable nature of these systems makes them appropriate for long-term drug delivery because they degrade gradually over time, eliminating the need for surgical removal. In addition, these systems can be customized to release medicines at specified rates and locations, enabling accurate dosing and limiting adverse effects.

In recent years, the development of biodegradable devices for IDDSs has been the subject of substantial investigation. Several biodegradable polymers, such as PLA (Da Silva et al., 2018), PGA (Li et al., 2020), and polycaprolactone (Yang et al., 2022), have been investigated by scientists to create IDDSs with distinct features (Table 1). Scientists also have investigated alternative drug-loading and −release mechanisms, such as integration of drugs into a polymer matrix (Siepmann and Siepmann 2012, Johnson et al., 2021) or reservoir system (Henry et al., 2019).

Biodegradable IDDSs have shown great potential in treating a variety of medical conditions. For example, these systems have been used to

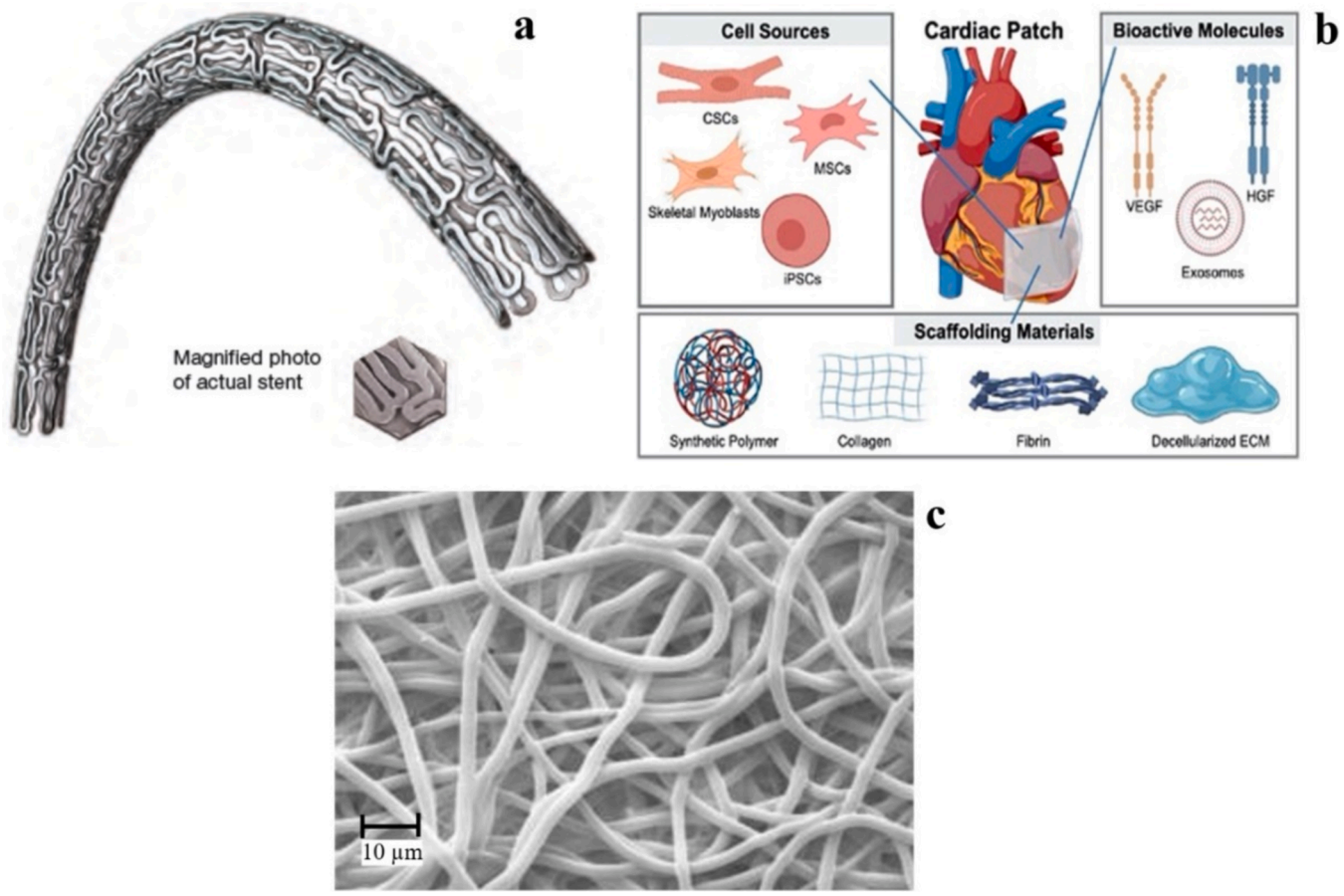

Fig. 3. Cardiovascular implants in different formats. (a) Xience V®, a metallic stent coated with everolimus (Reproduced from the US FDA Recently-Approved Devices, 2021. XIENCE Alpine Everolimus Eluting Coronary Stent Systems (XIENCE Alpine EECSS), XIENCE Sierra Everolimus Eluting Coronary Stent Systems (XIENCE Sierra EECSS), XIENCE Skypoint Everolimus Eluting Coronary Stent Systems (XIENCE Skypoint EECSS) – P110019/S115); (b) Cardiac patches (Reproduced from Xuan Mei and Ke Cheng, 2020. Recent Development in Therapeutic Cardiac Patches. *Frontiers in Cardiovascular Medicine*, 7:610364); (c) Vancomycin-loaded vascular grafts prepared by the electrospinning technique (Reproduced from Rossella Dorati et al., 2021. Tubular Electrospun Vancomycin-Loaded Vascular Grafts: Formulation Study and Physicochemical Characterizations. *Polymers*, 13(13), 2073).

deliver anticancer agents (Al-Zu'bi and Mohan, 2020), antibiotics (Ballard et al., 2019), analgesics (Svirskis et al., 2020), and hormones (Krovi et al., 2021). They have also been used to treat localized inflammation (Tan et al., 2020), infections (Pawar et al., 2019), and tissue regeneration (Liu et al., 2021). The ability of these systems to provide sustained drug release has been particularly useful for treating chronic conditions (Bhatia et al., 2022), such as diabetes (Abdelkader et al., 2021) and cardiovascular disease (Gupta et al., 2020, Toh et al., 2021).

6.2. *Microchip-based implantable drug delivery systems*

Microchip-based IDDSs (MIDDS) use a microchip to control the release of medication over time. MIDDS are typically implanted in the body and can be used to deliver a variety of drugs, including hormones, antibiotics, and chemotherapy drugs (Sutradhar and Sumi 2016). MIDDS have several advantages over traditional drug delivery methods. First, they can deliver drugs more precisely and accurately, which can help to improve patient compliance and reduce side effects. Second, MIDDS can be programmed for controlled release, which can be useful for treating chronic diseases or delivering drugs in response to specific triggers. Third, MIDDS are small and can be implanted in a minimally invasive procedure, which can reduce patient discomfort and recovery time (Staples 2010).

Numerous studies have shown the classification of IDDSs into two distinct types. The initial category comprises an active device, specifically a solid-state silicon microchip. The drug-releasing system can be regulated post-implantation through several mechanisms, such as mechanical, electrical, magnetic, laser, or alternative modalities. The second category is for passive devices or resorbable polymeric microchips. These types are predetermined drug-releasing systems that are determined by the materials, fabrication methods, or drug formulation. Once implanted, this system cannot be controlled. Fig. 4 shows active and passive time-released devices. The active system (Fig. 4a) consists of an anode reservoir cap and cathodes integrated into the substrate, allowing controlled release of the drug through externally triggered mechanisms such as electrical or magnetic signals. This setup provides precise and adjustable drug release based on the required dosage and timing. In contrast, the passive system (Fig. 4b) comprises a reservoir embedded within the substrate without external control, releasing the drug at a predetermined rate dictated by the material properties and environmental conditions. Both systems are designed for localized and sustained drug delivery, with active systems offering dynamic control over drug administration (Stevenson et al., 2012).

The permission granted by the US FDA to Proteus Digital Health for incorporation of ingestible microchips into pharmaceuticals is a notable progression in patient care and adherence to treatment. These dissolvable microchips enable real-time monitoring of medicine consumption, thereby aiding health-care professionals in optimizing treatment strategies. This development underscores a prevailing trend towards integrating cutting-edge technologies in the field of health care, with the potential to offer individualized methodologies aimed at enhancing

Table 1
Biodegradable polymers used in implantable drug delivery systems.

Polymers	Preparation and application	References
Polycaprolactone	• Fabrication of implantable drug delivery systems utilizing the hot-melt extrusion technique, with ibuprofen serving as the representative model medication. The drug-release efficiency rate can be > 99 % and be sustained for 120 h, mostly through the process of diffusion erosion.	(Yang et al., 2022)
PLGA	• Fabrication of a PLGA-based implant using the hot-melt extrusion technique, with incorporation of ibuprofen as the active pharmaceutical ingredient. The investigation revealed a distinctive drug-release pattern under all experimental conditions and comprised two phases: an initial phase with a constant drug-release rate, and a subsequent phase with an increased drug-release rate.	(Bassand et al., 2022)
Chitosan	• Successful application of the polycaprolactone/chitosan multilayer coating was achieved through the use of mechanical abrasion to increase adhesion. This application also revealed regulated patterns of antibiotic release. Notably, the films loaded with daptomycin demonstrated robust efficacy against both susceptible and drug-resistant strains of *Staphylococcus aureus*, indicating encouraging prospects for targeted treatment of localized infections.	(Soares et al., 2022)
PLA	• 3D printed PLA and polycaprolactone implants loaded with tetracycline showed antimicrobial properties against *Escherichia coli* and *S. aureus* for up to 21 days.	(Korelidou et al., 2022)

patient results (MedicalXpress, 2012). Another example is totally implantable access ports (TIAPs), which offer improved long-term central venous access for oncology treatments, but infections remain a concern due to biofilm growth. A 2022 innovation proposed a battery-free, wireless, smart TIAP with biochemical sensors for early infection detection by reading biomarkers through a smartphone with near-field communication capabilities, enhanced patient care, and reduced need for device removal. This advancement potentially can revolutionize monitoring and management of port-related infections (Gil et al., 2022).

6.3. Implantable pumps for drug delivery

For pump mechanism used in implantable drug delivery systems which are osmotic and infusion pumps. Osmotic pumps are specialized drug delivery systems that utilize osmotic pressure to achieve controlled drug release. They consist of a semipermeable membrane that allows water influx, creating pressure that drives the drug out at a constant rate, making them ideal for long-term therapies. Infusion pumps, on the other hand, use mechanical or electronic means to deliver precise drug doses over time, allowing for flexible and programmable release rates suited to patient-specific needs. Both systems enhance therapeutic efficacy by maintaining consistent drug levels, reducing dosing frequency, and improving patient compliance (Chappel 2021).

Many drugs require external rate and volume control. This control cannot be obtained with biodegradable or nonbiodegradable delivery technologies. Control of drug release has been recently achieved via small-pump systems (Cao et al., 2001). This control enables the patient to maintain a steady plasma concentration of the medicine for an extended duration. Fig. 5 show osmotic pumps (Fig. 5a), the drug-release mechanism of peristaltic pumps (Fig. 5b), and a general outside view of peristaltic pumps (Fig. 5c) and infusion pumps (Fig. 5d), respectively, and highlight the three pump mechanisms that have been developed and practically implemented in patients for present-day use (Pons-Faudoa et al., 2019).

Implantable pumps have been applied for several drug delivery systems and diseases. As demonstrated in Fig. 6, insulin-implanted pump devices or closed-loop controllers have been developed and used for managing type-1 diabetes (Renard 2002, Templer 2022). The implantable pumps are powered by batteries. The implants are stitched into a pocket of tissue directly under the patient's skin and are equipped with a catheter that pokes through the peritoneal wall to administer a steady stream of insulin directly into the patient's abdominal cavity to supply a constant amount of basal insulin directly into the peritoneal cavity, which makes the patient feel better, experience fewer insulin side effects, and provides greater dietary flexibility (Witkowski and Saudek 2008).

For implanted osmotic pumps, Hong et al. introduced a standard protocol used to induce aortic aneurysms via subcutaneous infusion of angiotensin II. The implanted osmotic pumps have been proven to work by subcutaneous implantation in mice (Lu et al., 2015). Infusion pumps have been used to deliver drugs directly into the cochlea. The implantable pump coupled to a cochlear implant electrode array ensures long-term delivery and effective dose control while allowing the use of many different drugs. The study demonstrated the viability of a drug delivery and pharmacokinetics model utilizing an active pump coupled to an electrode array, which could expand clinical and therapeutic approaches to inner-ear diseases (Manrique-Huarte et al., 2021).

6.4. Combination therapies

The term combination therapy–IDDS (CT–IDDS) refers to a specific

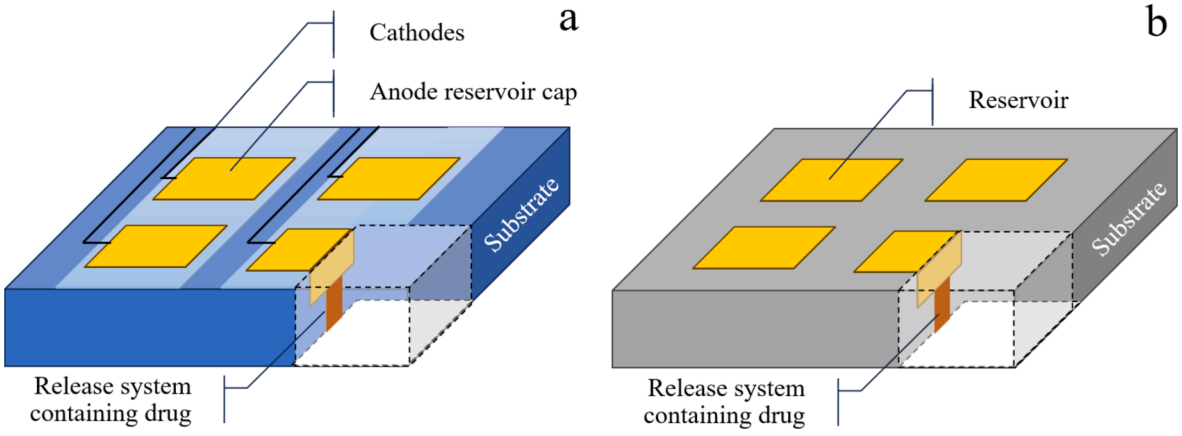

Fig. 4. Diagram of (a) active and (b) passive time-released microchip-based Implantable Drug Delivery Systems (IDDSs).

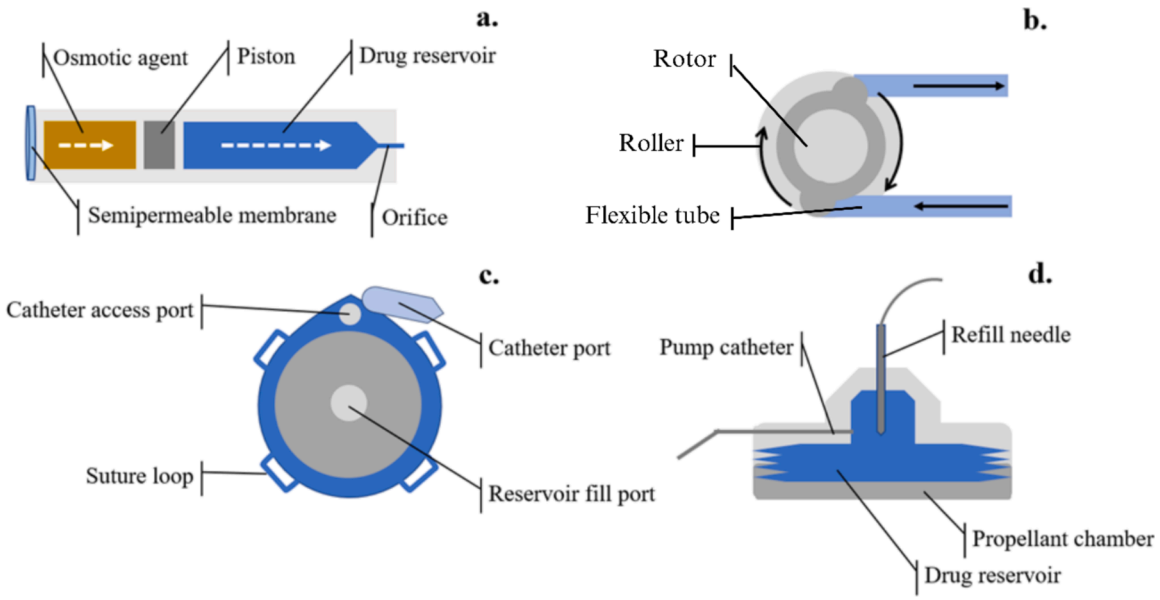

Fig. 5. Schematic of (a) osmotic pumps, (b) drug-release mechanism of peristaltic pumps, and (c) general outer view of peristaltic pumps and of (d) infusion pumps.

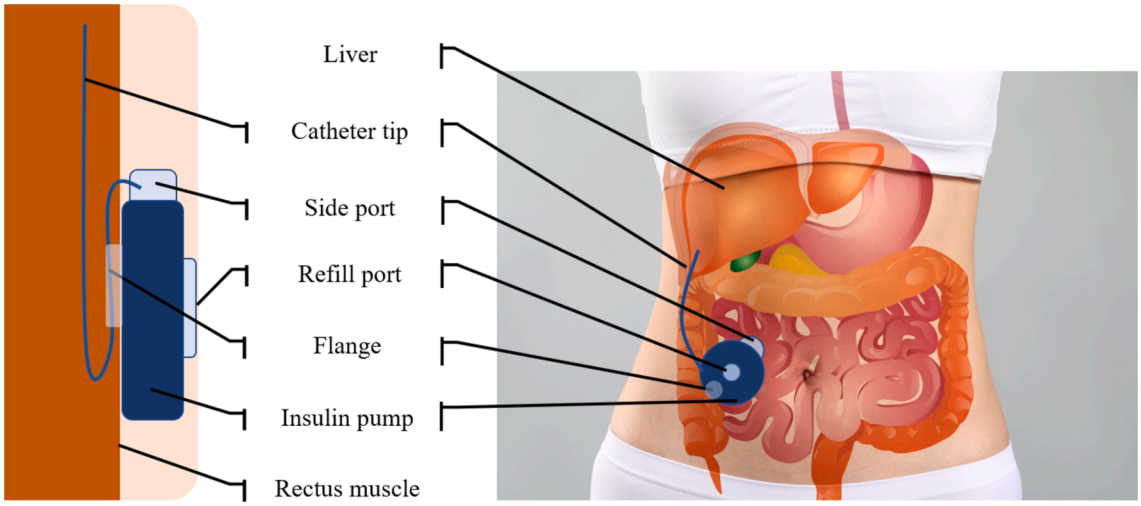

Fig. 6. Schematic view of the position of the insulin pump and catheter in vivo.

category of IDDSs designed to administer two or more drugs simultaneously. Various approaches can be used to enhance the efficacy of medications, minimize adverse effects, or selectively deliver pharmaceuticals to particular tissues or cells (Fayzullin et al., 2021). There are various methodologies for administering combination medicines through IDDSs. A commonly used strategy involves using a singular implant that houses multiple drug reservoirs. Regulated release of drugs from the reservoirs can occur either simultaneously or sequentially.

A CT–IDDS can potentially facilitate targeted delivery of chemotherapeutic agents to neoplastic growths, which can enhance treatment efficacy and mitigate adverse effects (Woodring et al., 2023). Muneer Al-Zu'bi and Ananda Mohan developed an extensive mathematical and computational framework to explicate the intricate dynamics involved in the local release and transportation of an anticancer medication within a thermally ablated solid tumor subsequent to introducing a dual-release implant (Al-Zu'bi and Mohan, 2020). Local triple-combination therapy, developed by João Conde and colleagues, involves the use of hydrogels loaded with gold nanospheres decorated with siRNAs and gold nanorods containing the anticancer drug bevacizumab (Avastin). This therapy was designed to induce tumor regression and prevent recurrence in a colon cancer mice model (Conde et al., 2016).

6.5. *3D printing*

In recent years, 3D printing technology has been used to develop implantable drug delivery devices that include intricate geometries and exhibit accurate drug-release profiles. Custom-designed devices can be tailored specifically to each patient, potentially enhancing therapeutic outcomes. Multiple implanted drugs have been created for various specialized uses (Table 2). PLA (Cui et al., 2021), polycaprolactone (Picco et al., 2022), and PGA (Yang et al., 2020) have commonly been used as the printing materials for fabricating IDDSs on 3D printers. Various printing techniques, such as fusion-deposition modeling (Cui et al., 2021), selective laser sintering (Wang et al., 2020), and extrusion-based 3D printing (Kim et al., 2022), have been used to fabricate these IDDS devices.

6.6. *Wireless control*

Certain IDDS devices now integrate wireless communication

Table 2
Research articles concerning 3D printed implantable drug delivery systems (IDDSs).

Model drug	3D printing technique	3D printing material	Specific application	Reference
Ciprofloxacin	Fused deposition modeling (FDM)	Polylactic acid (PLA)	Controlled-release implants with patient-specific microporosity, which is a novel strategy for treating bone infections.	(Cui et al., 2021)
Ifosfamide, methotrexate, and doxorubicin	Selective laser sintering	poly L-lactic acid (PLLA)	Treatment of osteosarcomas and to guide future clinical trials. The established techniques and principles can also be adapted to local chemotherapy for other tumors.	(Wang et al., 2020)
Methylene blue, ibuprofen sodium, and ibuprofen acid	FDM	PLA	Flexible and personalized hollow 3D printed implants with superior mechanical properties, consistent drug distribution, and modifiable release rates.	(Stewart et al., 2020)
Human insulin	Extrusion-based 3D printer	Polycaprolactone and lauric acid	3D printed multiunit implants that allow remote, light-controlled protein drug delivery (insulin) in response to near-infrared irradiation.	(Kim et al., 2022)
Olanzapine	Extrusion-based 3D printer	Poly(caprolactone)	IDDSs using robocasting 3D printing and a rate-controlling membrane to release the hydrophobic drug, olanzapine, for $\leq$ 190 days.	(Picco et al., 2022)
Lidocaine	Extrusion-based 3D printer	Polycaprolactone	Use of an extrusion-based 3D printer to manufacture sustained drug-release implants made of polycaprolactone, with a model drug (lidocaine) providing a potential solution to improve patient compliance.	(Liaskoni et al., 2021)
Olanzapine	Extrusion-based 3D printer	Polycaprolactone & poly (ethylene)glycol	Manufacture using 3D printing technology (robocasting) of subcutaneous implantable drug-eluting devices to achieve sustained drug release over a 200-day period.	(Picco et al., 2023)
Ciprofloxacin hydrochloride	Semisolid extrusion and FDM	PLA	Customized IDDSs made by use of 3D printing technologies to provide structural support for bone defects and controlled drug release.	(Cui et al., 2022)
5-fluorouracil, NVP-BEZ235	Extrusion-based 3D printer	PLGA	An orthotopic breast cancer drug delivery device using 3D printed PLGA scaffolds that reduces drug dosages, prolongs curative drug levels near tumor sites, minimizes exposure to normal tissues, and releases drugs long-term, potentially revolutionizing cancer treatment with precise, effective, and less invasive therapy.	(Yang et al., 2020)

technologies, allowing health-care personnel to remotely monitor and regulate drug administration. This approach may prove to be particularly advantageous for individuals with chronic diseases who require continuous medications. Rahimi et al. successfully engineered a micromachined drug delivery device that used wireless functionality via radiofrequency magnetic fields. This device incorporates microvalves composed of a poly(N-isopropylacrylamide) thermoresponsive hydrogel, which responds to a wireless resonant heater (Fig. 7). Consequently, the device enables accurate regulation of drug release by synchronizing the field frequency with the resonant frequency of the heater. This innovation holds promise for developing IDDSs that facilitate controlled TDD (Rahimi et al., 2011). Fong et al. (2015) also devised an active IDDS device that incorporates a microfluidic pump propelled by a radio-controlled actuator. This innovation enables accurate temporal drug administration through wireless activation via external radio-frequency electromagnetic fields. Consequently, this development potentially can provide comprehensive control and prolonged drug delivery within significantly reduced implant sizes. Moreover, it propels the advancement of personalized and localized drug delivery methods for individual patients (Fong et al., 2015).

6.7. Smart sensors

In the current technological landscape, there is a growing focus on the development of IDDS devices equipped with smart sensors and Internet of Things (IoT) technology, which refers to the interconnection of devices through the internet, allowing them to communicate, collect, and exchange data in real-time (Islam et al., 2016). In implantable drug delivery systems, IoT enables smart monitoring and control of drug release, enhancing patient outcomes through real-time adjustments and feedback for health-care providers (Fig. 8). This approach has the potential to enhance drug dose and safety, patient outcomes, and patient adherence (Raikar et al., 2023). Smart sensors generally work with implantable infusion pumps, implantable drug-eluting stents, and ingestible smart drug delivery devices (Raikar et al., 2023).

This technology has primarily been used to treat diabetes. Enabled by sophisticated materials and construction, wearable glucose sensors and implantable insulin delivery systems will revolutionize diabetes management (Zhang et al., 2021). Chu et al. developed glucose-responsive implantable microdevices for closed-loop insulin delivery and tested them in diabetic rats. Incorporating an albumin-based bio-inorganic membrane and microfabricated polydimethylsiloxane

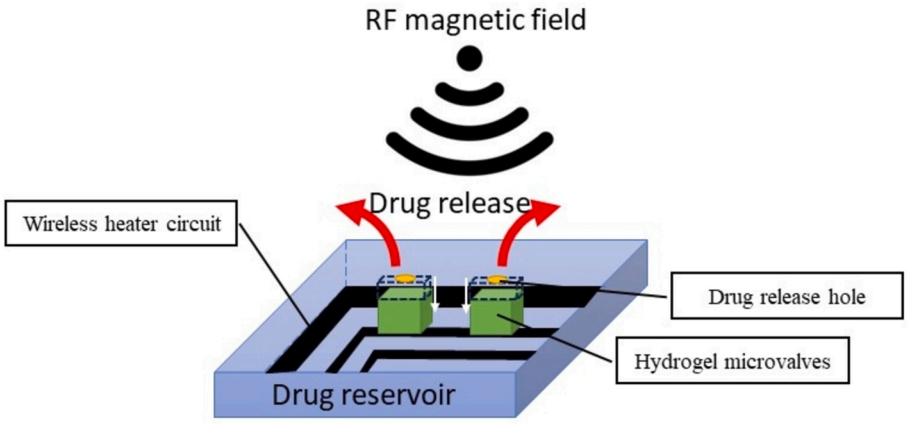

Fig. 7. Drug delivery device with frequency-controlled wireless hydrogel microvalves.

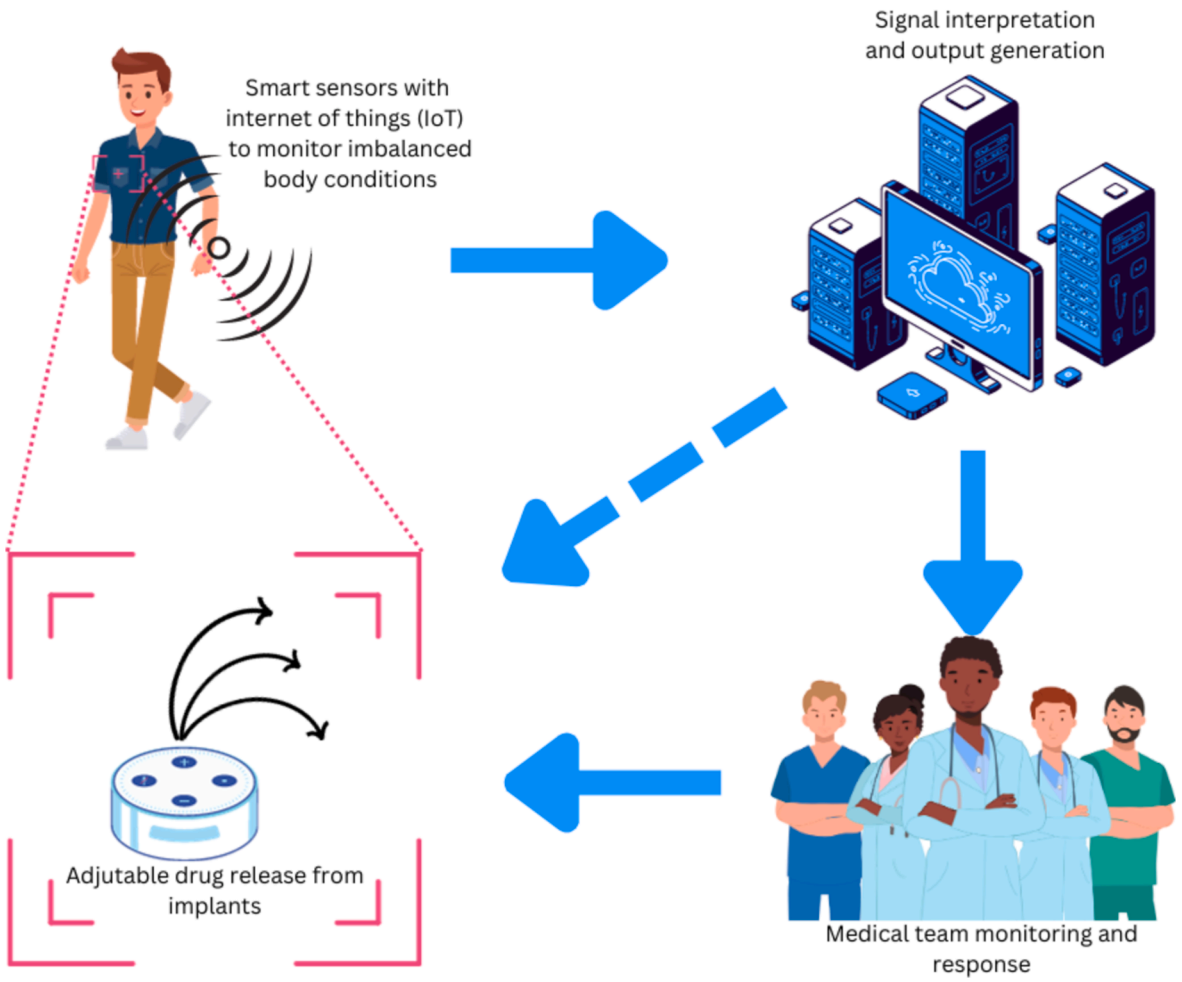

Fig. 8. Diagram illustrating the operational process of smart sensors and the Internet of Things for automated drug-release implants.

structures, the glucose-responsive implantable microdevices successfully demonstrated glucose-responsive insulin release during in vitro testing and effectively controlled hyperglycemia in diabetic rats over 1 week, showing their potential as efficient closed-loop biosensing and insulin-delivery devices (Chu et al., 2012).

6.8. Targeted drug delivery

IDDSs that can deliver drugs directly to specific tissues or organs in the body, such as the brain, spinal cord, or specific tissue are being developed (Gutman et al., 2000, Kaurav and Kapoor 2017, Smith et al., 2022). These IDDS devices can reduce the risk of side effects and improve treatment efficacy. Bai et al. developed antibiotic-loaded biodegradable implants prepared from poly(ε-caprolactone) for treating osteomyelitis, which is a local infection of bone tissue and marrow (Bai et al., 2020). Singh et al. also used alginate, sterculia gum polysaccharide, and polyvinylpyrrolidone in the formulation of a hydrogel intended for brain medication delivery implantation. The researchers discovered that the hydrogel could generate polymer films with porous characteristics. The drug-loaded polymer films gradually released the model drug, without any sudden burst effects. The release mechanism was shown to adhere to a Fickian-type behavior, which refers to the drug transport process in which the polymer relaxation time (t_r) is much greater than the characteristic solvent diffusion time (t_d) (Grassi and Grassi 2005), as evidenced by the best-fit first-order kinetic model. The polymer films were permeable to oxygen and water (Singh and Kumar 2020).

6.9. Microneedle implants

Microneedle implants represent a novel form of an IDDS that is under development. Microneedles are very small needles that are inserted into the skin to deliver drugs or other therapeutic agents. The microneedle implant consists of a biocompatible material that dissolves steadily over time, releasing the drug into the body. Microneedle implants have a number of advantages over traditional implants and injections. The insertion and removal of microneedle implants are less invasive and less agonizing. They are also more convenient because they can be self-administered by patients. In addition, microneedle implants can be used to deliver different drugs and therapeutic agents, such as proteins and peptides (Vora et al., 2021, Yang et al., 2022).

Microneedle implants have gained significant momentum in cardiovascular therapy, offering promising therapeutic benefits for various cardiovascular diseases, including hypertension, atherosclerosis, thrombus, and myocardial conditions (Zhou et al., 2022). These implants address the limitations of conventional drug delivery methods, such as intramyocardial injections and vascular devices, which are often hindered by short-term drug release and low retention at the targeted disease sites. The research team led by Yuwen Lu successfully designed microneedles that draw inspiration from the stingers of honeybees. These microneedles possess backward-facing barbs, which were incorporated to enhance tissue adherence in microneedle patches (Fig. 9). The adhesion performance of these microneedles, which are embedded in elastomer films, was improved by use of a spiral barbing pattern. During a demonstration of myocardial infarction treatment, the intervention was successfully applied to actively contracting hearts, resulting

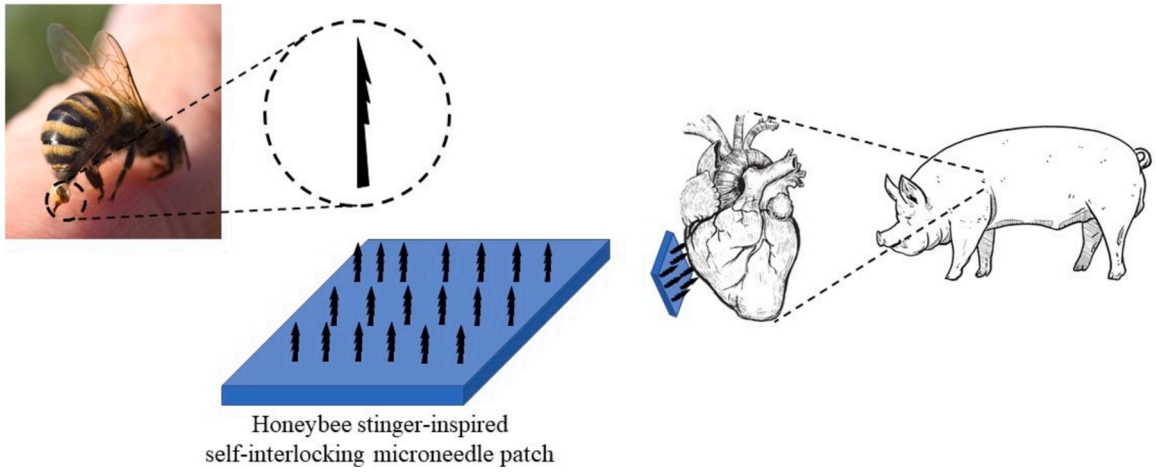

Fig. 9. Microneedles inspired from the stingers of honeybees for myocardial infarction treatment.

in reduced stress on the cardiac walls and preservation of ventricular function. This approach is a minimally invasive option for medical applications (Lu et al., 2022).

7. Clinical applications

Implantable drug delivery systems (IDDS) have a wide range of clinical applications, including the treatment of chronic diseases, pain management, cancer therapy, and contraception. These devices offer several advantages over conventional drug administration methods, such as improving patient compliance, reducing side effects, and enhancing clinical outcomes (Stewart et al., 2018). Table 3 provides examples of commercially available IDDSs, classified by type, materials, therapeutic uses, and action durations. A detailed explanation of the clinical applications of IDDS devices is provided below.

7.1. Chronic diseases

The majority of deaths globally are attributable to chronic diseases, and their incidence is projected to increase over the next decade (Alwan et al., 2010). When chronic conditions necessitate long-term treatment, the health-care system must meet the requirements of an expanding number of patients. Utilization of novel medication administration routes, particularly IDDS devices, has the potential to reduce clinical visits and follow-ups with health-care providers for treatment monitoring. Moreover, IDDS devices can be constructed to keep drug concentrations within the therapeutic window to achieve controlled continuous release of medicines over extended durations, hence reducing the possibility of patient noncompliance with oral medication. If the device is implanted in the afflicted tissue, a larger local medication concentration can be achieved, reducing systemic undesirable side effects, and decreasing the difficulties and discomfort of parenteral treatment.

IDDSs are frequently used to treat chronic diseases, such as diabetes (Bertsch and McKeirnan 2018), Parkinson's disease (TitanPharmaceuticals, 2018), and cardiovascular disease (Bourge et al., 2016). These devices can provide sustained drug delivery, ensuring that patients receive the correct medication dosage over an extended period, which can improve treatment efficacy and reduce the risk of medication non-compliance.

For example, ITCA 650, the first implantable, injection-free glucagon-like peptide 1 receptor agonist delivery device, uses the Medici Drug Delivery System™ (Intarcia Therapeutics, Inc., Massachusetts, USA) to achieve continuous delivery of exenatide, a drug for treating type 2 diabetes (Bertsch and McKeirnan 2018). The delivery device is a pump that maintains a steady release of exenatide over 6 months. Another example is ProNeura™ (Titan Pharmaceuticals, Inc., California, USA), which is a non-biodegradable rod composed of an ethylene vinyl acetate matrix and a drug formulation. The device has been used to deliver a dopamine agonist (ropinirole) and T3 for treating Parkinson's disease and hypothyroidism, respectively (Sreedharan et al., n.d., TitanPharmaceuticals, 2018).

Table 3
Examples of commercially available implantable drug delivery systems: classification by type, materials, therapeutic uses, and action durations.

Trade name	Generic name	Type of IDDSs	IDDS materials	Therapeutic application	Implant action duration	Reference
Nexplanon®	Levonorgestrel	Subdermal Implant	Non-biodegradable (Polymer)	Contraception	3 years	(Palomba et al., 2012)
Probuphine®	Buprenorphine	Subdermal Implant	Non-biodegradable	Opioid Dependence	6 months	(Smith et al., 2017)
Gliadel® Wafer	Carmustine	Implantable Wafer	Biodegradable Polymer	Brain Tumor (Glioblastoma), high-grade glioma	Immediate(within days)	(Perry et al., 2007)
Vivitrol®	Naltrexone	Extended-release Implant	Biodegradable Polymer	Alcohol, Opioid Dependence	1 month	(Syed and Keating 2013)
Implanon®	Etonogestrel	Subdermal Implant	Non-biodegradable	Contraception	3 years	(Le and Tsourounis 2001)
Viadur®	Leuprolide	Osmotic Pump Implant	Titanium Shell	Prostate Cancer	12 months	(Fowler Jr and Group, 2001)
Ozurdex®	Dexamethasone	Intravitreal Implant	Biodegradable Polymer	Diabetic Macular Edema, Uveitis	6 months	(Bansal et al., 2012)
SynchroMed™ II® pump	Morphine Sulfate	Infusion Pump Implant	Non-biodegradable (Titanium)	Severe Chronic Pain, Spasticity	Programmable	(Wesemann et al., 2014)
Vitrasert®	Ganciclovir	Intravitreal Implant	Non-biodegradable	Cytomegalovirus (CMV) Retinitis	5–8 months	(Christoforidis et al., 2012)

7.2. Pain management

IDDSs are also used for chronic pain management. These devices can deliver pain medication directly to the site of pain, reducing the need for frequent oral medication dosing, which can result in side effects, such as nausea and constipation (Ghafoor et al., 2007). David et al. used data from the Product Surveillance Registry to assess the risks and benefits of TDD via an intrathecal IDDS for chronic nonmalignant pain. The analysis included 4,646 patients who received TDD treatment between August 2003 and October 2019, with an average follow-up of 44 months. Site closures and patient fatalities accounted for 46.2 % of registry terminations, and adverse events and device-related issues accounted for only 10.2 %. These findings suggest that TDD may be a safer long-term alternative to systemic opioids for managing chronic pain, with enhanced patient acceptance and satisfaction, potentially reducing issues associated with opioid use in the management of chronic pain (Schultz et al., 2021).

Biodegradable polymer matrices have the potential to revolutionize postoperative pain management, but there is room for enhancement in the methods currently in use. The optimal device would biodegrade within a specified timeframe for pain classification while delivering drugs effectively during this time. In addition, this device should provide a suitable administration method tailored to specific applications and facilitate simple individualization for patients. Moreover, safety and resorbability are crucial material properties, and enhanced control over drug-release profiles is desired. Effective control of acute pain after surgery requires sustained relief for $>$ 24 h, and the high incidence of chronic pain development after major surgeries highlights the need for effectively managing acute pain. There is substantial demand for safer, more practicable, and more effective postoperative pain management practices utilizing biodegradable polymeric systems (Brigham et al., 2021).

7.3. Cancer treatment

IDDSs are also used for cancer treatment. These devices can be used to deliver chemotherapy drugs directly to the tumor, reducing the risk of systemic side effects and improving treatment efficacy. IDDSs can also be used to deliver targeted-therapy drugs, which are designed to attack specific cancer cells, reducing the risk of damage to healthy cells. Gliadel® wafers (Arbor Pharmaceuticals, Inc., Texas, USA), for example, are biodegradable wafers implanted in the brain to deliver the chemotherapeutic drug carmustine, which is an extremely effective chemotherapeutic agent but extremely harmful to healthy tissues. Gliadel® wafers reduce the toxicity of carmustine by directly transporting it to the tumor site. Gliadel® wafers enhanced survival in patients with recurrent glioblastoma multiforme, a type of brain cancer, according to a phase III clinical trial (Iuchi et al., 2022, Haim et al., 2023). Eligard® (Tolmar Therapeutics, Inc., Colorado, USA) is another example of an IDDS for treating cancer. Under-the-skin insertion of an Eligard® implant, which is non-biodegradable, delivers the hormone therapy drug leuprorelin acetate. By reducing testosterone levels, leuprorelin acetate is used to treat prostate cancer and advanced breast cancer. Eligard® was as effective as standard hormone therapy injections in the treatment of prostate cancer according to a phase III clinical trial. Eligard® was also more convenient for patients because it required only one injection every 12 weeks rather than the weekly injections required by conventional hormone therapy (de Freitas and Soares 2020, Abulateefeh 2023).

7.4. Contraception

IDDSs are also used as a form of contraception. These devices can be implanted under the skin and deliver a steady stream of hormones, preventing pregnancy for up to several years. The initial subdermal contraceptive implant, known as Norplant, consisted of a collection of six cylindrical rods that were designed to release levonorgestrel over a period of 5 years (Segal 1984). Norplant was first approved in Finland in 1983, followed by its subsequent approval in the United States in 1990 (Sivasankaran and Jonnalagadda 2021). Implanon® (Merck Sharp & Dohme, New Jersey, USA), a single-rod implant for 3-year contraception, was approved and marketed later in 2006. The 4-cm long and 2-mm diameter implant was composed of etonogestrel with an ethylene–vinyl acetate (EVA) copolymeric core and an EVA epidermis (Hohmann and Creinin 2007). In 2011, Nexplanon® (Merck Sharp & Dohme, New Jersey, USA), a radiopaque version of Implanon®, was introduced to enhance localization during removal (Al-Jawadi et al., 2018).

A number of new IDDSs are also in development for contraception. These new IDDSs use a variety of different technologies to deliver hormones to the body in a more targeted and effective manner. J. Long et al. developed a PVA hydrogel matrix entrapped with chitosan crosslinked microspheres of levonorgestrel (Fig. 10a). This delivery system holds promise for long-term contraception with controlled zero-order release behaviors (Long et al., 2019). Manoukian et al. (2018) sintered polycaprolactone–levonorgestrel microspheres to produce a cylindrical implant encapsulated in a polycaprolactone-based elastomer (Fig. 10b). Levonorgestrel's in vitro release was accurately characterized and determined to be Fickian diffusion-controlled, which demonstrated the use of elevated temperatures for accelerated-time drug-release studies (Manoukian et al., 2018).

7.5. Infectious diseases

IDDS devices are used in the therapeutic management of infectious disorders, including HIV/AIDS. These devices can provide antiretroviral medication directly to the specific location of infection, hence mitigating the likelihood of non-adherence to medication and enhancing the effectiveness of treatment (Flexner 2018). Several antiretroviral compounds have now been developed and formulated in the form of implantable drugs (Table 4).

7.6. Mental health

Research is currently being conducted on developing IDDS devices for the therapeutic management of mental health disorders, including schizophrenia and depression. These devices can administer drugs directly to the brain, thereby enhancing the effectiveness of treatment and minimizing the potentially adverse effects commonly associated with oral medication (Brewster et al., 2023). Hossain et al. successfully developed a drug delivery system consisting of multilayered cellulose acetate phthalate/Pluronic F-127 films for the encapsulation and interval delivery of 5HT2A agonists from a completely biodegradable and biocompatible implant. In vitro, the drug-loaded implant films exhibited three phases distinctly different from those of the multilayered cellulose acetate phthalate films (Hossain et al., 2023).

7.7. Ocular implant

The urgent need for development of an intraocular drug delivery system arises from the limited effectiveness of current pharmacological procedures in treating vitreoretinal illnesses. Current methods, such as eye drops and systemic drug administration, fail to achieve therapeutic drug concentrations within vitreoretinal tissue. This issue is addressed by intraocular drug delivery systems (Kaushal et al., 2023). Investigations of implantable devices or injectable microparticles for intraocular sustained-drug release have been conducted to address vitreoretinal disorders (Yasukawa et al., 2004). The initial utilization of a nonbiodegradable implant occurred in 1996 to treat cytomegalovirus retinitis as a result of acquired immunodeficiency syndrome. That investigation focused on biodegradable implants that were made of hydrophilic or hydrophobic polymers and shaped as rods, plugs, discs, or sheets (Yasukawa et al., 2006).

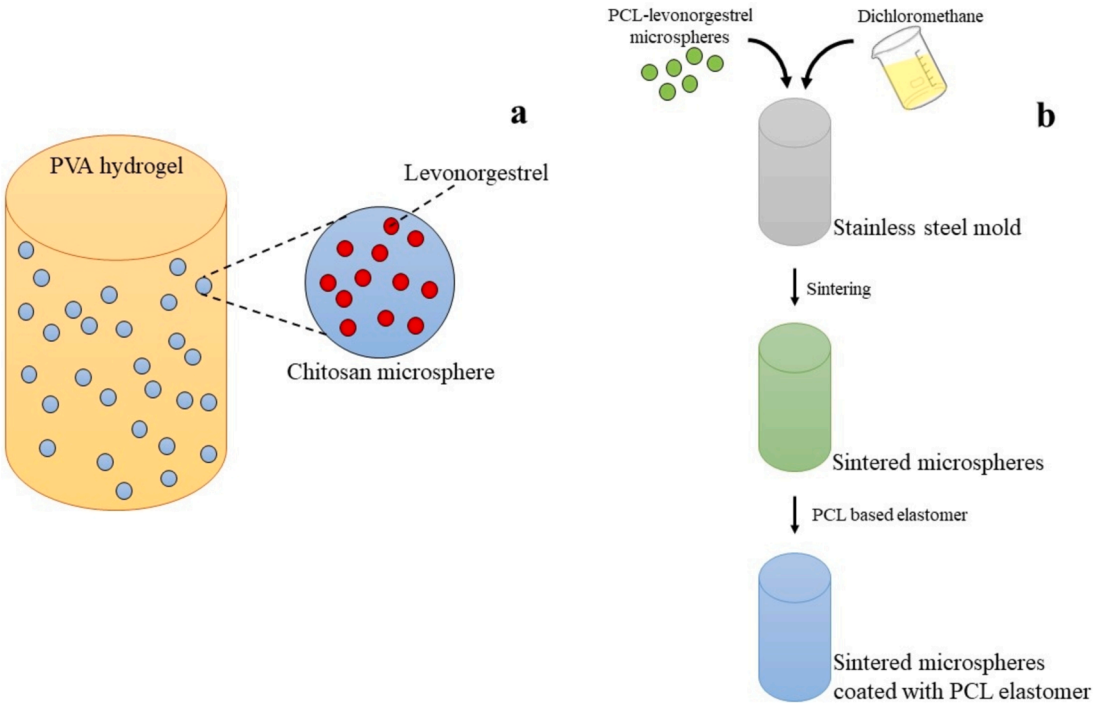

Fig. 10. Microsphere-embedded implant. (a) Polyvinyl alcohol (PVA) hydrogel matrix with entrapped crosslinked microspheres loaded with levonorgestrel (Long et al., 2019). (b) Polycaprolactone (PCL)–levonorgestrel microspheres chemically sintered and coated with elastomer (Manoukian et al., 2018).

Table 4
Research areas and related reports concerning the development of antiviral drugs in the dosage form of implants.

Antiviral drugs	Implant materials	Drug-release duration	Model animal	Reference
Nevirapine	Granulated drug core, PVA coating, permeable silicone tubes	90 days	Rats	(Chen et al., 2005)
Tenofovir alafenamide	Pure drug powder core, platinum microperforated silicone tubing, PVA coating	40 days	Beagle dogs	(Gunawardana et al., 2015)
Tenofovir alafenamide and emtricitabine	Titanium drug reservoir with a silicone nanochannel membrane	83 days for tenofovir alafenamide, 28 days for emtricitabine	Rhesus macaques	(Chua et al., 2018)
Entecavir	Biocompatible polymer blended with entecavir via hot-melt extrudates and polymer-coated tablets	87 days	Rats	(Henry et al., 2019)
Tenofovir alafenamide	Extruded tube of a biodegradable polymer, PCL, filled with model drug and castor oil	180 days	In vitro	(Johnson et al., 2019)
Dolutegravir	PLGA/NMP	>5 months	Humanized BLT mouse	(Kovarova et al., 2018)

Legend: PVA, polyvinyl alcohol; PCL, polycaprolactone; PLGA, poly(lactic-co-glycolic acid); NMP, N-methyl-pyrrolidone; BLT, bone marrow-liver-thymus.

A ganciclovir implant, commercially known as Vitrasert®, developed by Bausch & Lomb in Rochester, NY, USA, is a pioneering implantable device sanctioned by the US FDA for the therapeutic management of cytomegalovirus retinitis. The implant regulates release rates to ensure that the concentrations of active drug remains significantly below hazardous thresholds, an approach that can achieve higher drug concentrations while minimizing systemic adverse effects (Ebrahim et al., 2005). Following the initial success of the ganciclovir implant, a variety of biodegradable and non-biodegradable implants were either implemented in clinical practice or are now undergoing development (Kang-Mieler et al., 2020).

8. Challenges and future directions: Conclusions

IDDS devices are a promising approach for controlled drug delivery within the body and offer the possibility of enhanced efficacy. However, these devices present their own set of challenges. First, the invasive nature of the implants necessitates surgical implantation and removal, which carries risks and inconvenience. Second, it is essential to ensure biocompatibility to prevent adverse reactions. In addition, IDDSs devices must accomplish TDD, controlled drug release, and long-term stability. It is essential to address these requirements to realize the maximum potential of this technology.

IDDS devices are a rapidly developing technology with several promising directions despite the obstacles. Nanoparticles enable precise drug delivery to specific body sites and sustained release. As they naturally decompose over time, biodegradable substances eliminate the need for surgical removal. Intelligent IDDS devices can be programmed to release drugs in response to specific triggers, which provides greater precision. Individualized IDDS devices can be fabricated by 3D printers to meet the specific requirements of each patient.

Future innovations may include closed-loop IDDS devices that modify drug delivery rates on the basis of real-time patient monitoring, thereby improving accuracy. A multifunctional IDDS device can deliver multiple medicines or perform additional functions, such as imaging and diagnostics, thereby streamlining the treatment process. In conclusion, although IDDS devices can potentially revolutionize drug delivery, it is essential to overcome current obstacles. Ongoing research and development are concentrating on innovative solutions to improve the performance and safety of IDDS devices, bringing clinicians closer to fully

realizing the therapeutic potential of these devices in health care.

CRediT authorship contribution statement

Kampanart Huanbutta: Writing – original draft, Visualization, Supervision, Conceptualization. **Vivek Puri:** Writing – original draft. **Ameya Sharma:** Writing – original draft. **Inderbir Singh:** Writing – review & editing. **Pornsak Sriamornsak:** Writing – review & editing. **Tanikan Sangnim:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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