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Active implantable drug delivery systems: engineering factors, challenges, opportunities

Fabiana Del Bono, *[a] Nicola Di Trani, [b] Danilo Demarchi, [a] Alessandro Grattoni [b] and Paolo Motto Ros [a]

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Implantable drug delivery systems represent a transformative approach in modern pharmacology, offering precise and controlled drug administration tailored to individual patient needs. By circumventing physiological barriers such as the gastrointestinal tract and the blood–brain barrier, these systems enhance bioavailability and therapeutic efficacy while reducing systemic side effects. Key features include sustained or on-demand drug release, remote activation, and programmable dosing, which collectively improve patient compliance and minimize the frequency of interventions. Innovations in actuation mechanisms, powering technologies, and biocompatible materials have advanced the field, enabling the development of miniaturized, energy-efficient, and scalable devices. Applications range from chronic disease management to localized therapies for neurological and cardiovascular conditions. Despite significant progress, challenges remain in integrating power systems, communication protocols, and regulatory compliance for clinical translation. This review synthesizes the current state of active implantable drug delivery systems, discussing engineering trade-offs, system requirements, and future research directions toward achieving reliable, patient-centered solutions to guide system designers toward developing reliable, scalable, and patient-centered solutions that bridge the gap between cutting-edge research and clinical application.

1 Introduction

In the realm of modern healthcare, the quest for advanced drug delivery systems (DDS) that can precisely administer therapeutic agents to targeted sites while ensuring optimal patient compliance – adherence to prescribed treatments and health-related advice[1] – remains a crucial endeavor. Among

[a] *Department of Electronics and Telecommunications, Politecnico di Torino, Turin, TO, Italy. E-mail: fabiana.delbono@polito.it*
[b] *Department of Nanomedicine, Houston Methodist Research Institute, Houston, TX, USA*

Fabiana Del Bono

Fabiana Del Bono received her B. Sc. and M.Sc. in Biomedical Engineering from Politecnico di Torino in 2018 and 2020, and is currently pursuing a Ph.D. in Electronic Engineering at the same institution. Her research centers on the development and integration of active implantable systems for controlled drug delivery, with a focus on wireless power transfer, closed-loop operation, and in vivo validation. Additional interests include implantable interfaces for neuroprosthetics, addressing challenges in data transmission and system-level optimization for long-term therapeutic applications.

Nicola Di Trani

Nicola Di Trani received his B.S. and M.S. in Biomedical Engineering from Politecnico di Torino (2015, 2017) and a Ph.D. in Materials Science and Engineering from the University of Chinese Academy of Sciences (2021). He is currently a Postdoctoral Fellow in Dr. Alessandro Grattoni's lab at the Houston Methodist Research Institute. His research focuses on implantable drug delivery systems for chronic diseases including hypertension, cancer, and HIV PrEP. He has authored over 20 peer-reviewed publications in drug delivery, nanofluidics, materials science, and biomedical applications.

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these innovative approaches, implantable drug delivery systems (IDDS) have emerged as a promising solution. To grasp the landscape of drug delivery, it is essential to distill the main challenges faced by the field. Pharmacological treatments are an essential part of managing many diseases. The most prevalent chronic conditions necessitating pharmacological therapy encompass arthritis, hypertension, and diabetes.[2] Additionally, concurrent chronic obstructive pulmonary disease and heart failure mandate pharmacological intervention.[3] Chronic pain disorders requiring pharmacological therapy include neuropathic pain, low back pain, fibromyalgia, and osteoarthritis.[4]

Danilo Demarchi

Danilo Demarchi is Full Professor at Politecnico di Torino (DET), where he leads the eLiONS Lab and coordinates IIT@DET. His research focuses on smart system integration and IoT for AgriFood and biomedical applications, pioneering wearable plant sensors. He has held visiting positions at EPFL, Tel Aviv University, MIT, and Harvard Medical School. Founder and Editor-in-Chief of IEEE Transactions on AgriFood Electronics and co-founder of IEEE CAFE, he also leads the IEEE CAS AgriFood SIG. An IEEE CAS Distinguished Lecturer (2023–2024), he is active in BioCAS, Sensors Council, and OJ-EMB, and has chaired major IEEE conferences.

According to US government statistics, retail spending on prescription drugs in the United States constituted nearly 11% of total personal healthcare expenses in 2021.[6] Over the years, US expenditure on prescription medications has experienced significant growth, rising from $30 billion in 1980 to $335 billion in 2018.[7] Additionally, in 2019, the pharmaceutical sector in the United States saw a 5.4% increase in overall expenditures compared to the previous year, reaching a total of $507.9 billion.[8] Prior to the COVID-19 pandemic, controlled drug delivery systems were a substantial market, generating annual revenues exceeding $100 billion,[9] with the implantable drug delivery systems market identified as significant.[10] When speaking of pharmacotreatments, medication adherence – the degree to which patients follow their prescribed medication regimens[11] – significantly influences therapeutic outcomes, patient health, and healthcare costs, particularly in the management of chronic conditions. Patients with chronic conditions such as stroke, coronary heart disease, asthma, diabetes, hypercholesterolemia and rheumatoid arthritis frequently experience challenges in adhering to new medications and encounter difficulties in meeting their medication and information needs.[12] Polypharmacy, inappropriate prescribing, medication non-adherence, and adverse drug reactions are prevalent issues in managing chronic conditions.[13] Therapy adherence hovers around 50% in developed countries. Improving adherence with existing drugs could potentially have as significant an impact on outcomes as the introduction of new therapeutic agents,[14] being fundamental for therapeutic outcomes[15,16] and reducing risk of complications and hospitalization.[17,18] While increased medication adherence may lead to higher drug spending,[19] this is often counterbalanced by reductions in other healthcare costs such as hospitalizations and emergency department

Alessandro Grattoni

Alessandro Grattoni received his M.S. and Ph.D. in Mechanical and Biomedical Engineering from Politecnico di Torino, Italy. After postdoctoral training in nanotechnology at UT Health Houston, he joined the Houston Methodist Research Institute, where he is Professor, Chairman of Nanomedicine, and holds the Frank J. and Jean Raymond Centennial Chair. His research focuses on implantable systems for long-acting drug delivery and cell transplantation in HIV PrEP, metabolic disorders, and cancer. He also leads work on electrokinetic nanofluidics and 3D microencapsulation. Dr. Grattoni founded the Center for Space Nanomedicine and advises biotech startups Semper Therapeutics and NanoGland.

Paolo Motto Ros

Paolo Motto Ros: Assistant Professor at Politecnico di Torino. Circuits and systems, and smart system integration, for wireless implantable and wearable biomedical devices and applications; electronics for AgriFood. Senior Postdoc researcher at Istituto Italiano di Tecnologia (2014–2019) and Politecnico di Torino (2019–2022). ApplePies 2024 program co-chair; IEEE ICECS 2019, IEEE FoodCAS2021 (ISCAS2021), and IEEE CAFE 2023 organizing committee member; IEEE BioCAS 2021–2024 RCM, IEEE MeMeA2021 special session organizer, IEEE LASCAS2022/2023 PCM; MDPI Sensors guest editor and Frontiers in Neurorobotics guest associate editor. IEEE Transactions on Biomedical Circuits and Systems and IEEE Transactions on AgriFood Electronics Associate Editor.

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visits.[18,20,21] Traditional routes of drug administration encompass a range of methods, offering distinct advantages and limitations. Enteral and parenteral routes are conventional and widely utilized, while topical and transdermal routes provide localized treatment options.[22–24] However, these modalities may transiently induce toxicity states due to the necessity of administering quantified drug doses, leading to an initial surge in plasma concentration beyond the toxicity threshold, followed by transitions to the efficacy and ultimately inefficacy windows.[25] Traditional drug administration routes face challenges in controlling drug release and sustaining constant plasma therapeutic concentrations over extended periods.[26] Furthermore, they are hampered by biological barriers and off-target side effects.[27] Factors such as slow and incomplete dissolution, formation of insoluble complexes, poor net permeability, and first-pass metabolism limit oral drug absorption,[28] resulting in low bioavailability.[29] Challenges posed by biological barriers like the blood–retinal and blood–brain barriers drive innovations aimed at augmenting drug efficacy while mitigating side effects and enhancing patient compliance. These advancements hold significant promise for enhancing treatment outcomes across a multitude of diseases.[30–40]

Several diseases can benefit from timing drug administration to align with biological rhythms.[41] Chronotherapy is a therapeutic approach that aligns the timing of treatment with the body's natural biological rhythms, particularly the circadian rhythms, to enhance the efficacy and minimize the side effects of medications.[42] Coupled with the attainment of specific release profiles, it presents a promising avenue for optimizing drug delivery strategies. Chronopharmaceutical research is identified as a critical need, with the goal of developing customizable drug delivery systems tailored for chronotherapy. Such systems have the potential to enhance safety, efficacy, and patient compliance.[43] Pulsatile drug delivery systems are highlighted as particularly promising for chronotherapy, offering programmable drug release characterized by well-defined lag phases.[41]

Due to their significant social and economic impact, drug delivery systems that meet the aforementioned requirements are the subject of extensive research, involving diverse approaches and paradigms, widely investigated and reported in the literature.[44] Examining the history and taxonomy of drug delivery devices reveals that these systems have undergone substantial evolution over time, following different approaches and paradigms.

The development of implantable systems represents a specific segment within this broader landscape. Drug delivery implants represent a response to the imperative of enhancing patient compliance while maintaining drug concentrations within the therapeutic window.[9] Various authors have reported recent advances in the field, focusing on different strategies such as transdermal delivery,[45] fully implantable non-biodegradable devices,[46] desired profiles,[25,47] drug storage,[48,49] and application.[50–52] The emergence of digital health,[53] the widespread adoption of mHealth platforms with application in closed-loop treatments,[54] and even the prospects of space medicine[55] open up new horizons for the development and potential of these technologies. The rich scientific output evidences the diverse taxonomy of drug delivery implants, which can be categorized and analyzed from various perspectives, and ultimately reflects a shared effort in the literature and scientific endeavors to address specific therapeutic needs and challenges.

This review aims to offer a biomedical system engineering perspective in the specific field of fully implantable, active and externally controlled drug delivery devices, which to the best of our knowledge remains uncovered. These devices, hereby referred to as active implantable drug delivery systems (AIDDSs), represent a specialized subset of active implantable medical devices (AIMDs). An AIDDS is characterized by the presence of internal actuation or control mechanisms that actively regulate the release of a therapeutic agent. The term active refers to the fact that the device includes one or more energy-dependent subsystems that enable drug release to be modulated in a time-dependent, programmable, or stimulus-responsive manner. Unlike passive systems, which rely solely on natural diffusion, degradation, or osmotic gradients, active systems require energy input to trigger, sustain, or stop delivery functions. The designation system underscores the integration of multiple functional modules, including drug reservoirs, actuation units, control electronics, power sources, and often communication interfaces. As such, AIDDSs embody the convergence of pharmacological efficacy with engineered control, positioning them uniquely within the land-scape of implantable therapeutic technologies. As outlined in Fig. 1, AIDDSs exist at the intersection of active medical devices, implantable medical

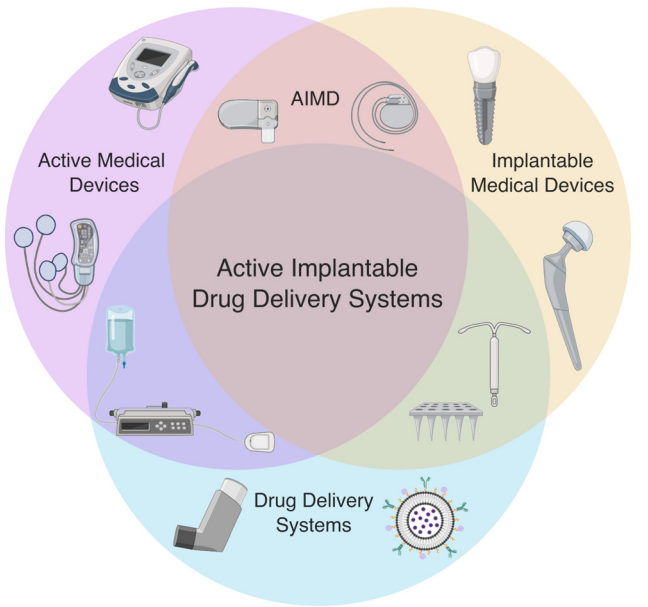

Fig. 1 Overview of medical and pharmaceutical systems. Active implantable drug delivery systems (AIDDSs) are a subset of active implantable medical devices (AIMDs), at the intersection of active medical devices, implantable medical devices and drug delivery systems. Created in BioRender.[5]

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devices, and drug delivery systems, with the distinguishing feature of incorporating a therapeutic agent and thereby qualifying as combination products. The first AIDDS emerged in the 1970s with the peristaltic infusion pump for continuous subcutaneous drug delivery. It enabled programmable, sustained release under external control, offering benefits like precise dosing and improved patient compliance. However, due to its bulk and limited battery life, it was mainly used in end-of-life palliative care, where portability was less critical. Despite its limitations, it laid the groundwork for future fully implantable and remotely controlled systems. In recent decades, research on actuators for implantable drug delivery technology has led to the development of numerous innovations in AIDDSs. This field offers significant therapeutic and commercial opportunities, as evidenced by the widespread regulatory approvals from FDA for partially-implanted commercial devices like Vyalev, iLet, and Omnipod.[56–58] The key milestones in the evolution of commercial AIDDSs are summarized in Fig. 2. However, many devices developed in basic research never reach the market. Additionally, a recent shift in focus has been observed, with increasing attention towards new transport mechanisms, formulations, and carriers for therapeutic agents.[47,59] For different reasons, AIDDSs still represent a research target for achieving the aforementioned challenges. First of all, while emerging biotechnologies and biomaterials show significant promise, their clinical translation readiness is yet to be fully established.[46] Active implantable drug delivery systems represent an alternative paradigm with respect to innovative formulations and carriers,[60] with the advantage of a faster pathway to clinical translation, supported by a more favorable regulatory framework. Second, from a systems engineering perspective, the advantage of AIMDs for controlled drug delivery lies in the availability of many actuation technologies. The scalability of dimensions and process transferability enabled by the use of MEMS in recent decades[61] has unlocked opportunities in this field with immense potential. While noteworthy and highly valid attempts have been made,[62] they have garnered little momentum and remain far from reaching the market. Progress in powering technology and remote communication adds up to this, making it possible to have complete devices and eventually seamless integration into the mHealth technological paradigm at the cost of taking up the challenges on integration and porting to mass production.[63] The objective of this article is to focus on the landscape of remotely controlled AIDDSs and to highlight the engineering milestones and challenges, to better clarify the opportunities offered by this drug delivery paradigm. This aims to provide system designers with guidance in navigating the landscape of AIDDSs, awareness of engineering trade-offs in designing such systems, and an understanding of what is needed to bring these devices to market. The article is thus structured as follows: section 2 discusses the essential engineering principles and design considerations, including system requirements, biocompatibility, and regulatory constraints. Section 3 reviews state-of-the-art technologies, categorizing solutions based on actuation mechanisms, powering methods, and communication strategies. Section 4 highlights fully developed systems from the literature, showcasing their applications, limitations, and potential for clinical translation. Section 5 synthesizes insights from the review, highlighting key opportunities for advancing implantable drug delivery systems. Section 5 discusses future trends and draws conclusions.

2 Engineering factors

Research in medical device technology, particularly drug delivery systems, typically begins with proof-of-concept studies and progresses toward clinical translation and market entry. The development of an AIMD for drug delivery must be addressed with a system engineering mindset, integrating comprehensive and systematic device design early in development to accelerate scaling to viable implantable technologies while minimizing design conflicts during later stages.

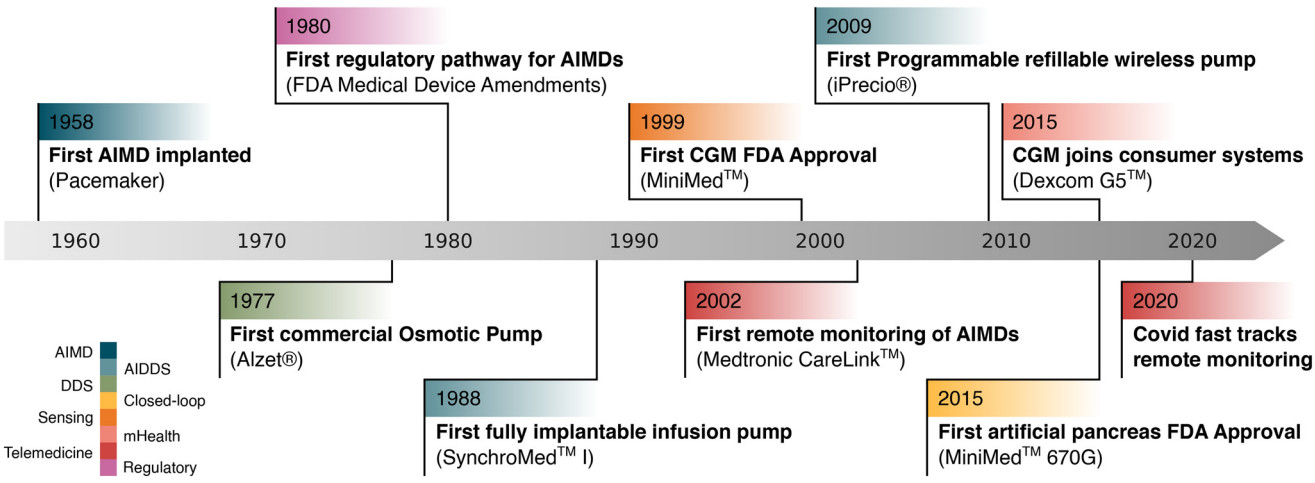

Fig. 2 Key milestones in the development of AIDDSs, including foundational technologies and related systems that have contributed to their evolution.

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Engineering a drug delivery device within a research setting encompasses a spectrum of activities spanning from basic research to translational research. In the realm of basic research, scientists delve into fundamental principles underlying drug delivery, exploring novel materials, mechanisms, and technologies. This foundational work lays the groundwork for innovation. However, as research progresses towards translational efforts, the focus must shift towards practical application, where collaboration across disciplines is paramount and a consistent design process must be followed.

Clinical translation refers to the process of advancing a medical technology from experimental validation to human application. For AIDDSs, this means demonstrating that the system can consistently deliver therapeutic agents *in vivo* under real-world constraints, while being safe, user-friendly, and compliant with medical device regulations. Adopting a translational mindset includes considerations of marketability, scalability, manufacturability, and regulatory approval, all while focusing on patient benefits.[64] Specifically, the engineering of AIDDSs integrates the multifaceted tasks required for designing any AIMD with the specific requirements and constraints inherent in the sector of pharmacological treatments. Applying effective design methods streamlines development, facilitating faster clinical translation while optimizing time and resources beyond the exploratory research phase. It is advantageous to offer a comprehensive overview of the ideal device development process.

2.1 Design process steps

An overview of the medical device design process, from ideation to market, is the following:

1. **Requirement analysis:** identify clinical needs, technical requirements, regulatory requirements, and safety considerations for the device.

2. **Conceptual design:** develop initial concepts of the device, including the drug release mechanism, power system, and control architecture.

3. **Feasibility study:** conduct preliminary studies to assess the feasibility of the design concepts, including initial prototyping and simulations.

4. **Detailed design:** refine the design details, selecting specific components, materials, software, and layout. Develop detailed schematics and models.

5. **Prototyping:** create functional prototypes to test and evaluate the device's performance, functionality, and safety.

6. **Preclinical testing:** perform *in vitro* and *in vivo* tests to assess the safety, efficacy, and biocompatibility of the device in animal models.

7. **Design optimization:** iterate on the design based on preclinical test results, optimizing for performance, safety, and manufacturability.

8. **Design verification and validation:** verify that the device meets design specifications and validate that it fulfills its intended purpose and complies with regulatory standards.

9. **Regulatory submission:** prepare and submit regulatory documentation, including preclinical and clinical data, to obtain approval from relevant authorities (*e.g.*, FDA, EMA).

10. **Clinical trials:** conduct clinical studies to evaluate the device's safety and effectiveness in human subjects, collecting data for regulatory submission.

11. **Manufacturing scale-up:** develop and optimize the manufacturing process for large-scale production, ensuring compliance with quality standards.

12. **Market launch:** release the device to the market following regulatory approval, with ongoing monitoring and support.

13. **Post-market surveillance:** continuously monitor the device's performance, safety, and efficacy in the market, gathering feedback and data to inform future improvements.

Steps 7 through 10 represent the core of the clinical translation process, where the device transitions from validated prototypes toward human application under regulatory and clinical constraints.

2.1.1 Clinical translation. Clinical translation of AIDDSs faces numerous challenges beyond technical feasibility. These include long and costly regulatory pathways, limited biocompatibility and long-term safety data, complexities in scaling up manufacturing, and misalignment between technical innovation and clinical or market needs. A common hurdle is the difficulty of integrating innovative actuation and control mechanisms into clinically usable and economically viable platforms. To address common bottlenecks in the clinical translation of implantable drug delivery devices, it is instructive to examine both successful and unsuccessful commercialization efforts. A prominent example of translational complexity is the microchip-based delivery system,[65] introduced in 1999 and later developed by the MIT spin-off Microchips Biotech. After a successful 2012 trial for osteoporosis treatment,[62] the company shifted focus to contraceptive applications.[66] However, regulatory complexity, usability challenges, and the need to adapt the system to new indications hindered progress. In 2019, Dare Bioscience acquired the company and repositioned the project (DARE-LARC1) at the preclinical stage, likely reflecting the need for further optimization before clinical translation.[67] In contrast, Intarcia's ITCA 650 – a matchstick-sized osmotic mini-pump for continuous exenatide delivery in type 2 diabetes – advanced through late-stage clinical trials[68] but failed to gain FDA approval due to manufacturing and safety concerns,[69] despite over a decade of development and significant investment. On the other hand, the MiniMed 780G by Medtronic,[70] approved in 2020, illustrates a successful path to market for automated insulin delivery.[71] Its success relied on progressive iteration, real-time glucose feedback integration based on standard and widespread communication protocols, and alignment with evolving regulatory expectations for closed-loop systems. These cases highlight key barriers such as device reliability, biocompatibility, regulatory clarity, and human factors engineering, all of which are critical for the successful clinical translation of advanced implantable systems. The devices analyzed in the following parts of this work, in most

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cases, are at the preclinical testing phase, often representing proof-of-concept prototypes or early-stage systems validated *in vitro* or in animal models. To do so, this work focuses on promising devices and technologies still in the research pipeline but exhibiting strong potential for clinical translation. By identifying common challenges and successful strategies, the review aims to guide future efforts in bridging the gap between laboratory innovation and real-world therapeutic application.

2.2 Design framework and development for AIMDs

Product design process models serve as a conceptual framework for designers, enabling them to adeptly navigate the intricacies of medical device development.[72] Utilizing iterative design and prototyping, addressing technical and clinical questions early on, and aligning with intellectual property and regulatory considerations is paramount to clinical success.[73,74] Relevant research has shown that the ideal medical device development stage-gate model progresses through phases including initiation, opportunity and risk analysis, formulation, concept and feasibility, design and development, verification and validation, and finally product launch and post-launch assessments.[75] Each phase can be iteratively performed, ensuring that each design issue is promptly addressed, minimizing time and resource loss. This process translates into moving from design inputs, consisting of clinical needs and regulations, to design outputs, which must be verified and validated before being transferred into a clinically translated product.[76] Following these steps, a device can move from discovery and basic research, through pre-clinical development, and towards clinical development and eventual market approval.[77]

2.3 The role of medical device regulations

A key challenge in the field of drug delivery is the regulatory landscape, which significantly impacts the market entry of many devices, even those in late development stages. Implantable drug delivery systems face regulatory challenges due to their variety and novelty. Regulatory directives, such as the medical device regulation (MDR) in the European Union and the stringent guidelines set forth by the Food and Drug Administration (FDA) in the United States, outline a series of steps and requisites for obtaining approval for products deemed safe and effective.[78] The regulatory classification determines their regulatory pathway and quality control requirements.[77]

The significance of these regulatory principles cannot be underestimated, even in basic research with translational aspirations, as they can accelerate development and reduce the risk of device failure.[74,75,79] Failure to consider these regulatory aspects early in the research may lead to developments that fail to meet regulatory standards for clinical translation, resulting in the loss of crucial safety and efficacy data necessary for evaluating novel therapeutic approaches.[76]

For drug delivery systems, acknowledging the combination nature of the product, and the overlap between medical device and pharmacological therapy regulations, facilitates better decision-making in the design of devices. Preferring implantable drug delivery systems compatible with existing drug therapies, which do not alter the drug formulation and only allow for better tailored dosing, timing, and release, is advantageous for faster clinical translation compared to investigating new formulations.[80]

2.4 From medical needs to system requirements: integration challenges

Central to the design process is the identification of system specifications derived from the medical needs of the intended use case. These integrate with consequent considerations such as size constraints, energy autonomy, and biocompatibility, which are fundamental to all active implantable devices, along with mandatory safety and efficacy requirements defined by regulations.

Biocompatibility is crucial for both short and long-term use, considering sterilization, thermal considerations, shape, and degradation products.[81,82] General safety, therapeutic effect, small scale, tunable release, and energetic autonomy are key factors,[83,84] to be joined with reduction of patient's burden, unobtrusiveness, and consideration of human factors.[85] Communication and security-privacy aspects, if applicable, must also be addressed.[86] The actuation, energetic autonomy, and communication are the most technologically constrained, and will be explored in section 3. These requirements should be integrated with the definition of the following, summarized in Fig. 3.

2.4.1 Site of action. An essential aspect in designing these systems involves determining whether systemic or localized drug delivery is optimal for the clinical application. Systemic delivery targets the bloodstream, facilitating broader therapeutic

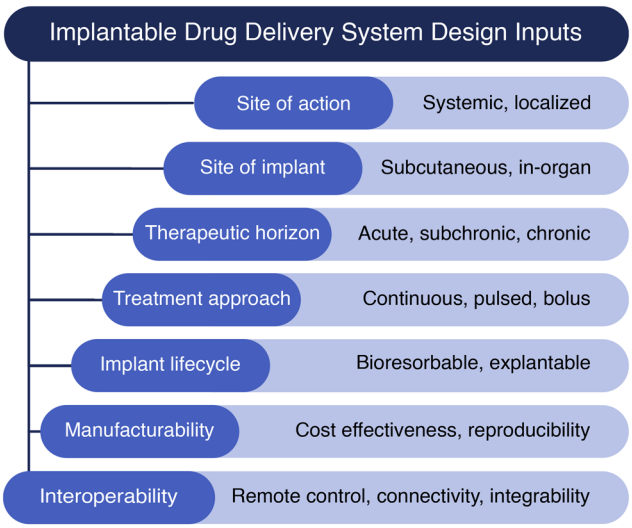

Fig. 3 Overview of the design considerations for an AIDDS.

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reach,[87–89] while localized delivery directs drugs to specific sites, minimizing exposure to healthy organs.[90–95] Each approach carries unique advantages and challenges, influencing implant site selection and subsequent design parameters.

2.4.2 Site of implantation. For systemic delivery, any site in communication with the bloodstream is viable. For localized delivery, the implant site can coincide with the delivery site or not. Subcutaneous implantation is popular and widely used in commercial applications, relating to refill possibilities, easier energy transfer, and explant procedures.[47,62,88,96] In-organ implant poses significant challenges in these terms, and explant or degradation may be necessary when the drug delivery function is over.[90,91,95,97,98]

2.4.3 Therapeutic horizon. Another critical factor in design is determining the duration of implantation. Devices designed for acute or subchronic drug delivery require short-lived implantation,[87,99,100] whereas those addressing chronic diseases demand prolonged implantation.[88,101] Other devices may be required for treatment of an acute condition that may occur anytime, requiring long-term implantation. This must be considered in conjunction with the implant lifecycle, explantation procedure, and energetic autonomy.

2.4.4 Treatment approaches. Release modalities, including continuous, pulsed, or bolus delivery, are customized to meet specific therapeutic requirements. These are closely connected with the actuation technology used.

2.4.5 Implantable device lifecycle. The lifecycle of an implantable device encompasses preimplantation, implantation, and explantation procedures, which must be harmonized with the device's intended duration and subsequent disposal. This influences the choice of materials that are sterilizable, stable, or eventually biodegradable. Additionally, scalability to mass production underscores the need for efficient and consistent manufacturing processes,[63] a requirement also endorsed by regulatory standards.

2.4.6 Manufacturability and cost. Cost-effectiveness and affordability are essential to enable broad adoption of AIDDSs, particularly in resource-limited settings. These factors must guide both system design and manufacturing. Using low-cost, scalable methods (*e.g.*, 3D printing, micro/nanofabrication), standard components, and industrially compatible materials reduces production costs. Modular design and simplified assembly improve efficiency, while long-lasting, rechargeable, or refillable devices lower the need for surgical replacements and long-term healthcare expenses. Aligning design and fabrication with economic and lifecycle sustainability supports clinical and commercial viability.

2.4.7 Interoperability and emerging paradigms. As healthcare shifts toward home-based and connected care, AIDDSs must be designed for seamless integration with remote monitoring systems, telemedicine platforms, and mHealth applications. Recent advances – such as MiniMed 780G,[70] Omnipod,[57] and Vyalev[56] systems – illustrate the growing demand for closed-loop and connected drug delivery solutions. These systems rely on continuous communication between sensors, pumps, and user interfaces, underscoring the importance of interoperability with standard communication protocols (*e.g.*, BLE, NFC, MICS), secure and compliant data handling, and energy-efficient operation. Such integration enables real-time therapy monitoring, remote adjustments, and improved adherence, supporting personalized medicine approaches. From a system-level perspective, it also contributes to cost-effectiveness, reducing hospital visits and enhancing chronic disease management. However, ensuring affordability and accessibility, particularly in resource-limited settings, remains a critical consideration during system design.

2.5 Design conflicts and trade-offs

During the translation of requirements into specifications, potential design conflicts may arise. These conflicts can include size constraints, the complexity of actuation mechanisms (such as peristaltic, pressurized gated, or simple diffusion systems), and energy transfer limitations. For example, opting for a refillable reservoir may limit implant depth due to refill access needs, while implanting a rechargeable device deeply may restrict available recharge methods. Generally, the more constraints involved, the more challenging the implementation becomes.

Ultimately, all these inputs converge into a design output that integrates possible solutions, balancing trade-offs to create a device with specified residency time, the presence or absence of a reservoir and its refill procedures, defined volume and volume efficiency, an appropriate release mechanism and technology, energy transfer or storage methodology, and potentially communication or trigger systems.

3 Current solutions

3.1 Release sites

3.1.1 Nervous system. Applications in the nervous system[94,102,103] require devices that are extremely small, wireless, and biocompatible to minimize tissue damage and support the natural movement of animals. These systems must enable precise, programmable release of drugs and are often combined with optogenetic stimuli. Common approaches include the use of flexible materials and low-power electrochemical micropumps, suitable for long-term experiments.

3.1.2 Circulatory system. Advanced drug delivery systems for the circulatory system[101,104] focus on on-demand drug release, often implemented on stents with energy transfer from external sources. Due to size constraints, reservoir-based approaches with integrated circuits are typically not feasible. Innovations include magnetic microrobots and controlled-release stents activated by ultrasound or electromagnetic fields. Techniques such as self-folding structures and resonant circuits enable precise and personalized drug administration, offering significant advantages for cardiovascular disease treatment. The presence of liquid in the circulatory system also provides an ideal medium for microrobot navigation and actuation.[104]

3.1.3 Gastrointestinal (GI) tract. Drug delivery devices for the GI tract[105–111] require features such as resistance to peristalsis,[106] active mechanisms, and miniaturization to fit

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into wireless capsule endoscopes. Most devices are designed for single-dose (bolus) administration, eliminating the need for refilling. Magnetic actuation using internal and external magnets facilitates precise movement and positioning. Advanced modules like electromagnetic actuators or gas-producing cells ensure controlled drug release, while localization sensors enhance real-time targeting for treating GI diseases. The fluidic environment of the GI tract allows microrobots to exploit the surrounding liquid for propulsion and controlled locomotion, supporting active navigation and targeted intervention.[112]

3.1.4 Ear. Drug delivery systems for auditory conditions face challenges such as limited cochlear access and the need to protect sensitive tissues.[93,113] Miniaturized, programmable devices with ultralow flow rates are required to ensure safe and precise administration. Solutions include wireless, biocompatible peristaltic pumps with activation capabilities. Miniaturization and electronic component integration are critical for effective clinical applications.

3.1.5 Ophthalmic applications. Drug delivery systems for retinal diseases like age-related macular degeneration and diabetic retinopathy[95,97,114,115] currently rely on intravitreal and subconjunctival injections, which are effective but limited by pain, side effects, and frequent administration. Implantable systems, such as battery-free magnetic pumps, enable precise and on-demand drug release, reducing injection frequency and improving patient compliance while minimizing complications.

3.1.6 Subcutaneous applications. Subcutaneous systems are generally associated with either systemic drug delivery or localized delivery to specific organs *via* catheters, as seen in intrathecal drug delivery.[47,62,87,92,116–121] These systems aim for controlled, on-demand drug release to optimize therapeutic efficacy and reduce side effects. Solutions include stimulus-responsive materials (*e.g.*, magnetic fields, NIR light), reservoir systems with adjustable membranes for personalized dosing, and electrofluidic technologies to minimize power consumption. Wireless devices also support chronotherapy, synchronizing administration with circadian rhythms to improve patient adherence. Adjustable valves enhance drug delivery capacity without requiring pumps, while piezoelectric actuators and pressure sensors enable multidose and multidrug administration, improving analgesic efficacy. Integrated sensors provide precise and regulated dosing, reducing errors and side effects.

3.1.7 General purpose devices. Some devices are designed for generalized localized delivery, with their implantation sites not explicitly reported in the literature. However, the implantation site and device design are closely interconnected, as each imposes constraints on the other.

3.2 Drug release strategy and pattern

Drug delivery devices can actuate drug release with different strategies and patterns. The drug release strategy can involve active processes, where energy is converted to drive the release, or passive methods, where diffusion or pressure gradients naturally enable drug transport, often following the rupture of a barrier. In some cases, the release can be modulated by integrating components that regulate the flow, such as valves or membranes that respond to specific triggers, allowing for greater control over the timing and dosage.

The drug release pattern reflects how the drug is administered over time. This can manifest as a continuous flow, ensuring a steady release over a prolonged period, or as discrete events where the drug is delivered in a single bolus or at defined intervals in a pulsed manner. In general, release change in pattern is designed to occur on-demand, allowing for external or internal cues to initiate or modify delivery, providing a dynamic and responsive approach tailored to patient needs or physiological conditions.

3.3 Release actuation technology

The release technology often represents the central focus of research on these systems and serves as the core around which the requirements are defined. This section highlights various implementation strategies found in the literature for controlled and triggerable drug release.

Drug delivery systems primarily rely on transport mechanisms to transfer drugs from the device to the physiological environment. The main mechanisms for controlled release can be categorized into two broad approaches: passive diffusion with molecular passage modulation and pressure gradient-driven release. These approaches are implemented in various practical ways. Passive diffusion can be controlled through the opening and closing of channels to achieve specific release profiles. Alternatively, the dissolution or state change of a carrier material allows the passage of drug molecules previously contained within. Pressure gradient-based release is implemented through peristaltic pumps or pressurized reservoirs. Pressurization may involve maintaining a constant internal pressure while modifying the fluid's resistance through valves or dynamically regulating the reservoir pressure to generate the required gradient in real time. These transport strategies are explored further in the subsequent sections. Some examples are represented in Fig. 4.

3.3.1 Heating-mediated delivery. Thermal processes are exploited for drug delivery by employing thermosensitive materials in various configurations. These methods must comply with regulatory limits to ensure safety *in vivo*, particularly regarding the thermal propagation to the biological environment. Heating-based strategies include electrothermal dissolution of parylene or titanium/platinum valves in both pressurized and non-pressurized reservoirs.[62,115,118] Phase changes in materials, such as gallium, can generate propelling forces within reservoirs,[122] while shape-memory alloys create deflections that expel drugs.[124,125] Thermal expansion of PDMS has also been utilized.[102] Additionally, thermosensitive coatings, such as those on drug-emulsified stent layers, can release drugs when heated *via* resonance.[101] Many devices rely on radiofrequency excitation to generate the required heat

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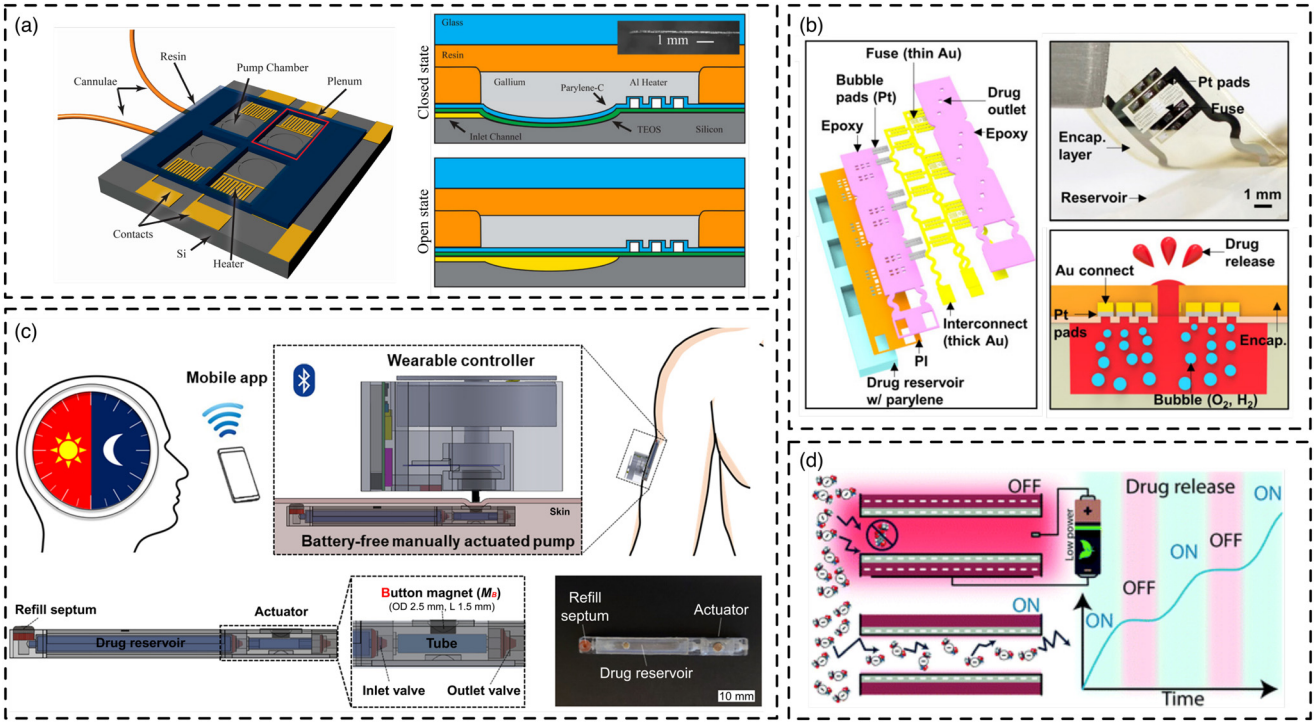

Fig. 4 Examples of actuation technologies relying on different approaches: (a) heating-mediated delivery based on a shape-memory polymer, reproduced from ref. 122 with permission from MDPI, copyright 2016; (b) electrolysis delivery based on pressure, reproduced from ref. 89 with permission from AAAS, copyright 2021; (c) magnetically actuated device based on tube compression, reproduced from ref. 120 with permission from AAAS, copyright 2021; (d) electrically controlled delivery through nanochannels in a silicon membrane, reproduced from ref. 123 with permission from RSC, copyright 2020.

internally, using coil structures that bypass the need for internal power sources and complex control circuits.

3.3.2 Electrolysis delivery. Electrolysis-based systems operate through two main mechanisms: gas generation and dissolvable membranes. Micropumps generate gas bubbles *via* electrolysis, creating pressure that pushes the drug from the reservoir into surrounding tissues.[62,89,94,95,97,103,116,126–133] By modulating the applied voltage, the duration and speed of drug release can be controlled, supporting pulsatile or sustained release profiles. These systems often allow for reversible chemical reactions. Once the drug is released, body fluids refill the reservoir, dissolving a solid drug dose for subsequent delivery, a method known as the solid drug refill (SDR) approach.[129] Alternatively, dissolvable membranes made from materials such as magnesium[87] or gold[65] can connect the reservoir to the biological environment through electrolytic dissolution, enabling drug diffusion. These two approaches can also be combined, integrating pressure generation with barrier dissolution to enhance release performance.[134]

3.3.3 Electrically responsive materials. Electrically responsive materials offer precise control over drug delivery. Polypyrrole (PPy), for instance, can release negatively charged molecules by adjusting the applied voltage or current, enabling on-demand or cyclic drug delivery. PPy nanoparticles were recently used within a potentiostat, allowing for on-demand drug delivery.[91] Another use of PPy involved coupling it with dodecylbenzenesulfonate anion in a membrane with regular pore size and density.[135] Thanks to this material, pore size is modulated by the applied voltage, and thus is drug flow. Similar approach but based on a different principle sees a silicon nanofluidic membrane working as an ionic field effect transistor.[88,123,136,137] The physical principle of drug modulation in this device relies on controlling molecular transport through nanochannels by using a gate electrode. By applying a low-energy electric field, the device can adjust the surface charge of the nanochannels, which, in turn, affects the movement of charged drug molecules.

3.3.4 Piezoelectric delivery. Piezoelectric materials, changing shape with an applied electric potential, facilitate the miniaturization of actuators and have been used in various drug delivery mechanisms, since earlier designs. These include peristaltic pumps,[138–140] two-stage pumping systems,[96] and microvalves for on-demand activation from pressurized reservoirs.[92,121,141] Piezoelectric devices offer precise control and compact designs, but their power consumption, typically in the range of tens to hundreds of milliwatts, often necessitates external power sources, such as direct wiring or implanted batteries.

3.3.5 Magnetically actuated delivery. Magnetically actuated drug delivery systems rely on magnetic interactions for operation. Some devices use solenoids to generate magnetic fields that drive plunger movements for reservoir pumping.[119,120,142] Static magnetic fields have also been

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employed to open and close valves, allowing controlled drug release.[115] For ingestible capsules, soft magnets enable selective opening and release through repulsion forces generated by demagnetization and remagnetization.[109] Other designs use an external magnetic field to control delivery mechanisms, such as slider-crank systems within ingestible capsules.[111] Magnetic materials embedded in osmotic devices, such as superparamagnetic iron oxide (SPIO) particles, can generate heat within membranes.[143] This heat activates particles like PNIPAM, which shrink in size, increasing membrane porosity and enabling flux regulation under an alternating magnetic field. While magnetically actuated devices require careful characterization, they provide simple and efficient flow control with minimal reliance on power transfer.

3.3.6 Ultrasound-mediated drug release. Ultrasound-triggered systems leverage non-invasive acoustic energy to achieve targeted, controlled, and on-demand drug release. Ultrasound can induce release through thermal effects, acoustic cavitation, or mechanical stress, depending on carrier design and ultrasound parameters.[144–146] Various responsive materials and carriers have been explored, including liposomes, hydrogels, and microcapsules.[147] These systems enable localized activation at depth within tissues, thereby minimizing systemic drug exposure and enhancing therapeutic precision. Magnetically navigable microrobots operating in the circulatory system have been proposed as ultrasound-responsive platforms for drug delivery, allowing precise targeting *via* magnetic guidance and subsequent ultrasound-mediated drug release.[104] Such actuation simplifies the implant architecture – facilitating deeper implantation – though it requires more complex external hardware to generate and control the acoustic signals.

3.3.7 Other methodologies. Several alternative methodologies for active drug delivery, though less represented in the literature, have shown promising results. Examples include micromotors and spring-loaded systems,[106,108,110] microthrusters that utilize combustion to propel drugs,[105] and light at near-infrared (NIR) frequencies to alter membrane porosity and enhance reservoir flow.[87] Each of these approaches offers unique mechanisms to address specific challenges in drug delivery. Recently, the integration of engineered living materials with bioelectronic platforms is enabling adaptive, self-regulated therapies. Coupling living cells with responsive interfaces allows programmable release of therapeutic exosomes for tissue regeneration.[148] Engineered cells can also be triggered by light or electrical signals to secrete proteins like insulin or cytokines, enabling precise, closed-loop delivery.[149] Electroactive microbes and cells further act as biosensors, logic gates or actuators for autonomous intervention,[150,151] reflecting the growing synergy between bioelectronics and synthetic biology.[149]

3.4 Use of reservoirs

Many drug delivery devices in the literature rely on reservoir systems for drug storage and release, particularly when alternative strategies, such as material property changes enabling molecular release, are not employed. Reservoir-based systems allow for controlled drug release over time, reducing the frequency of administration and improving patient adherence to treatments. The introduction of transcutaneous refill capabilities further extends the duration of drug release without requiring repeated surgical interventions, a feature primarily applicable to devices with superficial implantation sites.[88]

Reservoir-based devices can be designed for various release profiles. Some are optimized for sustained release, while others enable on-demand, pulsed releases. In certain cases, they deliver single-dose drug "shots" after which the device terminates its function. When designing active reservoir-based systems, the volume of the reservoir relative to the total device volume defines the volume efficiency (η_{vol}), which measures the usable volume of the device. Maximizing volume efficiency is crucial for enhancing biocompatibility, reducing invasiveness, and minimizing the obtrusiveness of the device.

Key factors contributing to increased η_{vol} include the miniaturization of the actuation system, as discussed earlier, and the powering methods, which are analyzed in the following section.[152] The possibility for transcutaneous refill further extends the IDDS lifespan, avoiding surgical replacement and extending the possibility for continuous treatment.[153] A summary of the reservoir-based devices found in the literature is reported in Table 1.

3.5 Powering technology

Powering technologies for AIDDSs are crucial for ensuring the long-term functionality and reliability of therapeutic and diagnostic systems.[156] These devices, which include drug delivery systems, neurostimulators, and biosensors, often require energy sources that are compact, biocompatible, and capable of sustaining operations over extended periods. Traditional battery-powered implants have been widely used, but they pose challenges in terms of size, longevity, and the need for surgical replacement or recharging. As a result, there has been significant progress in the development of alternative powering methods that offer greater efficiency and longevity. Several authors have provided comprehensive reviews on the field of biomedical engineering.[157–161] Wireless power transfer (WPT) techniques, such as capacitive and inductive coupling[162] and radiofrequency (RF) energy harvesting, have emerged as promising solutions, enabling devices to be powered or recharged without the need for invasive procedures. Ultrasound and optical energy transfer methods are also being explored for their ability to reach deep implants with minimal energy loss.[161] Additionally, advances in energy harvesting technologies allow devices to harness energy from the body's own physiological processes, such as heat, movement, or bioelectric signals, to power microelectronic components. Piezoelectric and triboelectric materials have been leveraged to convert mechanical energy

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Table 1 Devices with reservoirs

Ref.	Year	Release strategy	Release pattern	Actuation technology	Powering (communication) technology	Volume (mm^3)	η_{vol}%
96	2008	Active	Sustained/pulsed	Piezoelectric	Rech. battery + inductive (IR interface)		[b]
134[a]	2009	Active	One-shot	Electrolytic degradation and pumping	—	222.6	6.74
105	2010	Active	One-shot	Thruster	Battery (RF)	786.5	89.00
141	2010	Modulated	Pulsed	Osmotic + piezoelectric valve	Battery (N/A)	137 160.0	[b]30.00
62	2012	Passive	Multiple-shot	Electrothermal ablation	Battery		
126[a]	2012	Active	Sustained/pulsed	Electrolytic pumping	—		[b]
106	2013	Active	One-shot	Mechanical	Battery (RF)		
127[a]	2014	Active	Pulsed	Electrolytic pumping	Inductive (ASK on WPT)		
47[a]	2014	Modulated	Pulsed	Thermoresponsive membrane + NIR laser	—		
97	2014	Active	Sustained	Electrolytic pumping	Rech. battery (N/A)		[b]
124	2015	Active	Pulsed	Shape-memory alloy	RF	220.5	[b]34.47
107	2015	Active	One-shot	Electromagnetic coil + permanent magnets	Rech. battery (RF)	786.5	38.14
130[a]	2015	Active	Pulsed	Electrolytic pumping	—		
143	2015	Modulated	Sustained/pulsed	Osmotic + thermoresponsive membrane	External alternating magnetic field		
154[a]	2016	Active	Sustained/pulsed	Electroresponsive polymer	Ultrasonic		
118	2016	Active	Sustained/pulsed	Electrolytic pumping	Inductive (telemetry on WPT)	2430.0	[b]7.61
109	2016	Active	One-shot	Magnetic	External solenoid	1188.0	65.66
131	2016	Active	Pulsed	Electrolytic pumping	US	770.0	1.69
114[a]	2017	Active	Sustained/pulsed	Electrolytic pumping	Triboelectric nanogenerator		[b]
132[a]	2017	Active	Sustained/pulsed	Electrolytic pumping	Near-field resonant inductive coupling		[b]
125	2017	Active	Pulsed	Shape-memory polymer	RF	125.0	4.00
102	2017	Active	One-shot	Thermal expansion of composite	RF	125.0	58.48
119	2018	Active	Pulsed	Magnetic	—		
115	2018	Active	Pulsed	Magnetic	—	105.0	11.90
111	2018	Passive	Pulsed	Magnetic	—		
93	2019	Active	Sustained	Peristaltic based on phase-change	Rech. battery (BLE)		
155	2019	Active	One-shot/pulsed	Electrolytic pumping	Inductive	16.4	23.20
87	2020	Passive	Multiple-shot	Electrolytic degradation	Inductive		
89	2021	Passive	One-shot	Electrolytic degradation	RF	250.0	48.00
120	2021	Active	Pulsed	Mechanical + external solenoid	Ext. battery (N/A)	184.0	[b]81.52
133[a]	2021	Active	Pulsed	Electrolytic pumping	DC power supply		[b]
99	2023	Passive	Multiple-shot	Electrolytic degradation	Biodegradable battery (light trigger)		

[a] Not complete devices. [b] Refillable reservoirs.

from body movement into electrical power, offering a self-sustaining solution for long-term implantation.[163]

Recent efforts have explored the use of magnetoelectric (ME) materials to further miniaturize receiver modules in implantable systems. ME structures can operate efficiently at smaller scales compared to traditional inductive coils, making them attractive for compact device integration[164] light-based powering has also emerged as a promising approach, using visible to near-infrared (NIR) wavelengths captured by photodiodes, photovoltaic elements,[165] or through photothermal conversion.[166] These methods may help reduce tissue heating and improve biocompatibility, but remain in an early development phase, with ongoing efforts aimed at overcoming power transfer and penetration limitations. These innovations in powering technologies are essential for expanding the capabilities of implantable devices, reducing the need for invasive maintenance, and improving patient outcomes. However, challenges such as power efficiency, safety, miniaturization, and biocompatibility continue to drive ongoing research in this field.[167] This section analyzes the powering methods applied to IDDDs. Fig. 5 graphically illustrates the size and power consumption requirements of devices available in the literature, some of which are already equipped with powering solutions, and relates them to a representation of the powering methods generally available in the field of AIMDs.

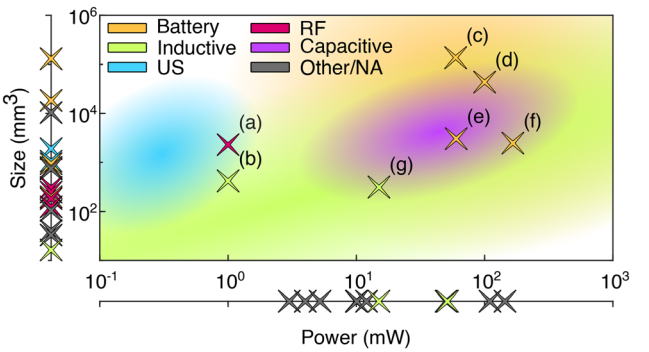

Fig. 5 Size and power consumptions of devices in the state of the art: (a) ref. 95, (b) ref. 118, (c) ref. 92, (d) ref. 96, (e) ref. 108 (f) ref. 105 and (g) ref. 103 report both size and power consumption. Colored areas in the background indicate qualitatively available powering technologies in the literature.

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3.5.1 Batteries. Batteries provide a reliable, long-term energy source for devices and are often essential for applications requiring high instantaneous power.[168] However, their size and need for explantation after depletion are a downside. Rechargeable (secondary) batteries address this limitation by reducing device size, though they have a lower energy density and require an additional recharging system. Thermal processes during recharging must also be carefully controlled to ensure safety. Reservoir-based systems powered by batteries generally exhibit low volume efficiency due to the volume occupied by the battery and the associated energy conversion or actuation circuitry. Primary battery-powered devices are common in implantable drug delivery,[47,92,105,106,108,110,113,118,142] while secondary batteries are also used.[93,96,121] External wearable power transfer systems, which transfer energy to implanted devices, have also been explored,[119] offering improved volume efficiency through optimized designs. Reported power consumption for battery-powered devices in this field ranges from 60 to 166 mW. Additionally, certain externally powered release technologies are compatible with battery integration for future use.[129,133,139] These systems are generally designed for superficial implantation or for use in gastrointestinal capsules.

3.5.2 Inductive power transfer. Wireless power transfer (WPT) using inductive coupling leverages electromagnetic induction to transfer energy between a transmitting and receiving coil through a variable magnetic field. This method enables charging or powering devices without physical connections, reducing infection risks and enhancing patient comfort. Inductive power transfer (IPT) is a commonly used technique for wireless power transmission in implantable medical devices due to its robustness, simplicity, safety, and opportunity for simultaneous and bidirectional data and power transmission.[162] Resonant tuning of the coils, such as using near-field resonant inductive coupling (NRIC), improves efficiency and operational distance. However, NRIC requires precise coil alignment and is sensitive to interference from materials affecting the magnetic field. Inductive power transfer systems can be optimized by adjusting coil size, number of turns, operating frequency, coil spacing, geometry, material properties, and transmitted power. This technology is particularly popular in drug delivery, enabling battery-free operation and on-demand system activation while minimizing device size.[62,91,94,103,127,128,132] Reported power consumption for these systems ranges from 1 to 50 mW.[62,103,121,127,128]

3.5.3 Radio frequency (RF) power transfer. RF-based wireless power transfer (WPT) offers the advantage of transmitting energy over greater distances compared to inductive or capacitive methods. Key benefits include the absence of physical contact and improved tolerance to misalignment. However, RF transfer has lower energy efficiency, greater energy dissipation in tissues, and increased susceptibility to electromagnetic interference. It is best suited for low-power, long-distance applications but less ideal for rapid charging or highly efficient energy transfer. RF powering is utilized in many experimental drug delivery devices, often coupled with simplified and compact receiving circuits.[89,95,101,102,115,124,125] While received power is rarely reported, transmitted power typically ranges from 0.05 to 2 W.

3.5.4 Ultrasound-based power transfer. Ultrasound-based wireless power transfer (WPT) uses acoustic waves emitted by an external piezoelectric transducer. These waves propagate through biological tissues to an implanted receiver, which converts acoustic energy into electrical energy to power medical devices or recharge their batteries. This method allows significant miniaturization of the receiver and is suitable for powering deeply implanted devices.[169] However, the continuity of the medium (*e.g.*, the presence of coupling gel) is critical for effective acoustic wave transmission. Drug delivery devices using ultrasound-based powering are relatively recent, with few examples in the literature. Reported energy requirements, when specified, are typically in the range of hundreds of microwatts.[90,91,131,154]

3.6 Remote communication methods

The communication methods employed in implantable drug delivery systems can be categorized as either relying on the same technology as the energy transfer system, or not. Among the methods relying on energy transfer, modulations on energy transfer *via* NFC are notable,[94,103] together with amplitude-shift keying (ASK) modulation on inductive power transfer.[127] Communication methods that operate independently include generic RF communication,[105] communication in the MICS band,[62] and Bluetooth low energy communication.[88,113]

4 Complete systems from the state of the art

In this section, we highlight exemplary systems from the literature that showcase clever and thoughtful integration across various engineering domains. These designs are strategically developed to stay within close reach of regulatory requirements, offering realistic pathways to clinical translation and paving the way for scalable and clinically impactful drug delivery solutions. These examples serve as benchmarks for understanding current progress and as inspiration for further innovation in the field. Table 2 summarizes the main trade-offs and challenges associated with the devices discussed in the remainder of this section, highlighting their advantages and disadvantages, as well as the challenges on technical implementation and regulatory considerations that have been addressed or remain open, respectively.

4.1 Soft implantable device for treatment of seizures

Joo *et al.*[89] designed a soft implantable device (SID) (Fig. 6a) for seizure treatment, continuously monitoring EEG signals and using wireless power transmission to trigger drug release during emergencies. The minimally invasive subcutaneous implantation allows rapid pharmacological intervention while bypassing skin barriers. Although not a replacement for conventional methods, the SID addresses critical situations requiring swift and targeted responses. Currently, the device

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Table 2 Comparison of devices in terms of trade-offs and challenges

Device	Trade-offs	Challenges
4.1 (ref. 89)	(+) highly responsive; integration with sensing (−) not refillable; wearable instrumentation always on	(T) Alignment of WPT; system development/integration; (R) management after use to be addressed; high complexity complicates certification
4.2 (ref. 87)	(+) Bioresorbable; on-demand; multi-reservoir; (−) limited programmability; single-use; limited residency time	(T) Optimisation of material corrosion; RF tuning; low-cost process; (R) byproduct safety and toxicity studies; lack of standardization complicates certification
4.2 (ref. 99)	(+) Bioresorbable; self-powered; selectable multi reservoir; (−) single use; limited programmability	(T) Creation of biodegradable battery; calibration of photoselectivity; (R) byproduct safety and toxicity studies; lack of standardization complicates certification
4.3 (ref. 94)	(+) dual use – optogenetics and pharmacology; multiple drugs; (−) limited by receiver depth and use of wearable	(T) Encapsulation; addressable reservoir activation; RF coupling; miniaturization; refill missing; (R) dual use complicates certification; longer term tests needed
4.4 (ref. 110)	(+) targeted release; endoscopy-compatible; expellable; (−) single-use; mechanical assembly complexity	(T) Safe thermal activation; miniaturized rotating parts; flow optimization (R) missing biocompatibility studies; complex fabrication; evaluation of cost-effectiveness
4.5 (ref. 133)	(+) integrated dose sensor; simple; low-cost (−) limited delivered volume; limited programmability	(T) Fabrication with carbon ink within PDMS; simple wireless activation; (R) certification of included materials; *in vivo* validation needed
4.6 (ref. 113)	(+) wireless, refillable, programmable; consistent manufacturing; (−) limited battery; no feedback	(T) Fine flux control; miniaturization; optimization of fabrication; recharge missing; (R) implant > 6 mo. reached; extension for chronic use needed
4.7 (ref. 91)	(+) deep implant, localized release; on-demand (−) anionic drugs only; not refillable; limited programmability	(T) Drug retention optimization; system design for consistent release; (R) definition of explant procedures; sterilization and certification of used materials
4.8 (ref. 88)	(+) sustained release; remote control; low-power; refillable; (−) limited battery; assembly complexity	(T) System miniaturization; power consumption optimization; innovative actuator design; (R) need for chronic testing; addressing standardization of assembly/sterilization

Legend: (+) = advantages; (−) = disadvantages; (T) = technical addressed challenges; (R) = regulatory challenge considerations.

must be explanted after use, but future developments may include bioabsorbable or degradable materials to simplify its management after drug depletion.

4.2 Bioresorbable, on-demand devices

Koo *et al.*[87] (Fig. 6b-i) introduced a bioresorbable, self-powered device. Drug release is triggered by specific light frequencies that activate photodiodes, creating a short circuit in the biodegradable electrochemical cell, and causing the degradation of anodes covering the reservoirs. Similarly, Zhang *et al.*[99] (Fig. 6b-ii) presented a bioresorbable device for wirelessly controlled drug delivery, utilizing active valves based on electrochemically triggered crevice corrosion for precise drug release, powered with inductive transfer. The bioresorbable nature of these devices eliminates the need for surgical removal post-treatment, reducing associated risks. These systems are suitable for applications requiring shallow implantation and localized, on-demand, and time-sensitive drug delivery, particularly in acute scenarios, after which the device naturally degrades.

4.3 Battery-free optofluidic microsystem for neural research

Zhang *et al.*[94] (Fig. 6c) presented a compact, wireless, battery-free optofluidic microsystem designed for studying neural circuits in freely moving animals. Combining pharmacology and optogenetics, the device integrates an electrochemical micropump for drug delivery, refillable reservoirs for multiple administrations, and a micro-LED for programmable optogenetic stimulation with precise control of light frequency and intensity. Powered *via* near-field communication (NFC), the system eliminates the need for batteries. Its soft, flexible design minimizes tissue damage, making it suitable for long-term experiments without repeated trauma. The design is scalable and supports integration into closed-loop systems for real-time monitoring and manipulation of neuronal activity.

4.4 Next-generation wireless endoscopic capsule

Woods *et al.*[110] (Fig. 6d) introduced a next-generation wireless endoscopic capsule designed for targeted drug delivery in the intestinal tract. The capsule features a conical compression spring made of stainless steel, which, when fully compressed, generates enough force to release the stored drug through a needle operated by a mechanical system. The device integrates an RF controller, a camera for imaging, and is powered by a battery, enabling precise and controlled drug administration. This system represents an example of a microrobotic platform operating within the gastrointestinal tract.

4.5 Electrolytic drug delivery device with integrated monitoring

Yi *et al.*[133] introduced an electrolytic drug delivery device that uses electrolysis-induced bubble expansion to deform a polydimethylsiloxane (PDMS) membrane, driving precise drug release. A flexible piezoresistive sensor integrated into

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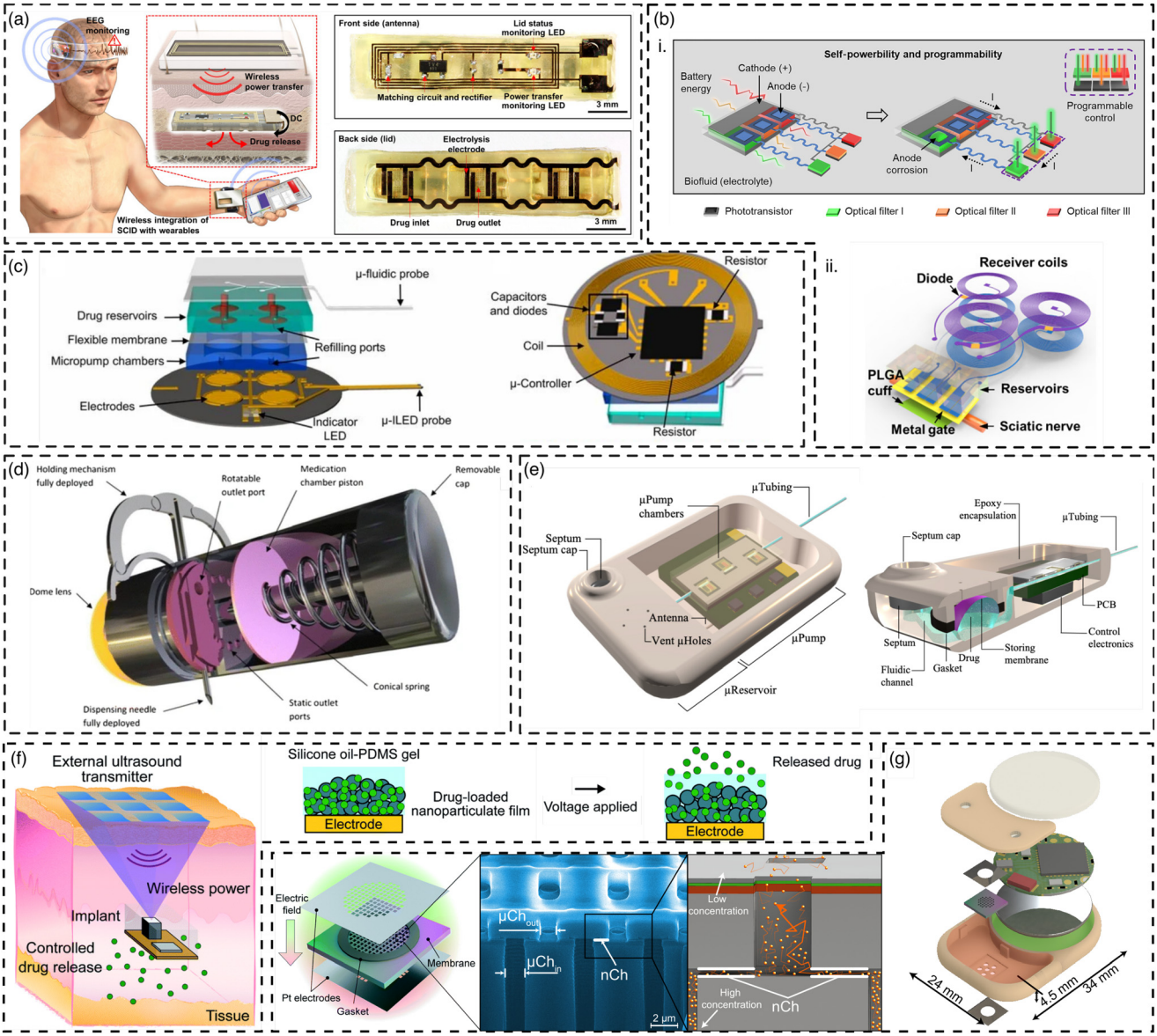

Fig. 6 Examples of successful integration of complete active drug delivery systems: (a) soft implantable device for the treatment of seizures, reproduced from ref. 89 with permission from AAAS, copyright 2021; (b) bioresorbable and i. self-powered system, reproduced from ref. 87 with permission from AAAS, copyright 2020; ii. inductively activated system, reproduced from ref. 99 with permission from PNAS, copyright 2023; (c) battery-free multireservoir system for neural research, reproduced from ref. 94 with permission from PNAS, copyright 2019; (d) wireless endoscopic capsule for drug delivery, reproduced from ref. 108 with permission from Wiley, copyright 2015; (e) 3D printed peristaltic drug delivery system, reproduced from ref. 113 with permission from MDPI, copyright 2021; (f) ultrasound-activated drug delivery system, reproduced from ref. 91 with permission from RSC, copyright 2022; (g) electrically controlled nanochannel delivery system, reproduced from ref. 88 with permission from RSC, copyright 2019.

the membrane enables real-time monitoring of drug volume and flow rate with high accuracy. The device ensures controlled flow rates, reducing risks of overdose or underdelivery, and is optimized for small-scale drug volumes, making it ideal for micro-dosing applications. It is particularly suited for localized treatments in ophthalmology, neurology, and cancer therapies. The system envisions telemetry and wireless power transfer for remote monitoring and control, while currently focusing on *in situ* dosage sensing.

4.6 Miniaturized 3D-printed drug delivery system

Forouzandeh *et al.*[113] (Fig. 6e) presented a miniaturized drug delivery microsystem fabricated through 3D printing and wirelessly controllable. The device features a refillable microreservoir and a peristaltic micropump based on phase-change materials, suitable for subcutaneous implants and transdermal applications. The system's structure is fabricated using stereolithography with biocompatible resins, while the micropump is directly integrated onto the back of a printed

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circuit board using inkjet printing technology. It is powered by a rechargeable battery, although no charging system is included, and offers Bluetooth connectivity for remote control.

4.7 Ultrasound-activated drug delivery system

Wang *et al.*[91] (Fig. 6f) introduced a wireless, miniaturized drug delivery mechanism (DDM) for localized release, powered by an external ultrasound transmitter. Ultrasound waves are converted into electrical energy by a piezoelectric receiver, triggering electrochemical reduction in a PPy nanoparticulate film to release negatively charged drugs. The system is designed for deep tissue implantation and is particularly suited for rapid or localized drug delivery in severe hypoglycemia, localized cancer therapy, and epilepsy. While it eliminates bulky batteries and invasive procedures, its effectiveness depends on precise transmitter alignment, and its drug storage capacity is limited and non-refillable. Wang *et al.*[170] build upon this design with a closed-loop control mechanism that measures redox currents during drug release and transmits this feedback to an external controller. This allows to dynamically adjust the potentiostat's voltage in real-time and improves precision to meet therapeutic needs.

4.8 Electrically controlled drug delivery system

Di Trani *et al.*[88] (Fig. 6g) presented a subcutaneous drug delivery device designed for chronic disease management. The system uses a silicon-based nanofluidic membrane to mediate drug release *via* concentration-driven diffusion from a refillable reservoir, modulated by a low-intensity electric field applied through platinum electrodes. The device has a battery powered electronic control system, and modulation of drug release is achieved thanks to remote control with Bluetooth low energy. The device supports continuous drug administration, avoiding the fluctuations typical of pulsatile systems, which improves treatment efficacy. Subsequent work was done to address the biocompatibility of the actuation mechanism[123,171] and to recharge the device to extend its useful life to years.[172,173]

5 Discussion on active DDS research progress

Reservoir-based drug delivery systems provide a versatile and promising approach for treating diseases, particularly chronic conditions. As outlined in Table 1, these systems support a wide range of release profiles, including continuous and on-demand drug delivery. Devices with refill capabilities are particularly advantageous as they allow for indefinite usage, making them suitable for chronic diseases requiring sustained treatment and reducing the need for invasive procedures. This flexibility often necessitates superficial implantation to facilitate refilling, aligning well with the needs of chronic disease management. Their compatibility with various actuation technologies further broadens clinical applications, offering customized solutions for different therapeutic needs.

Batteries currently represent the most reliable and widely used power source, offering consistent and possibly long-term (but still limited) energy delivery. However, as the size of devices is reduced, batteries often occupy a disproportionate share of the device's volume, creating a barrier to further miniaturization. The use of secondary batteries allows for battery miniaturization, without reducing, instead increasing (virtually to infinity) the overall device residency time within the body thanks to their rechargeability. The necessity of both recharging batteries and power batteryless devices has led to growing interest in alternative powering methods, such as wireless power transfer and energy harvesting, which can enable smaller and less invasive designs without sacrificing functionality. Inductive and radiofrequency systems are gaining popularity for their ability to facilitate miniaturization and simultaneous communication, though they necessitate external instrumentation for power supply. Capacitive coupling, despite its promise in terms of power delivery and size compatibility, is underreported in the context of drug delivery systems. Ultrasound-based systems are rarely implemented, and their reliance on external transducers and gel mediums for efficient energy transfer presents significant challenges to large-scale diffusion. Though rarely addressed in the literature, addressing power-related challenges early in the design phase is essential for the development of scalable and clinically viable devices. An important but often overlooked aspect is the security of these devices. While enabling technologies have been the focus, once a certain level of development has been reached, it will be essential to incorporate security considerations into the iterative design process to support safe remote access and data integrity.

Successful examples of system integration in drug delivery devices combine the harmonization of actuation mechanisms and power supply with applicability and product and lifecycle considerations for *in vivo* considerations, providing valuable guidance for future developments. Examples from the literature show that achieving this integration enhances clinical applicability and supports scalability to mass production. Additionally, system fabrication and scalability to mass production remain critical considerations. Simplifying device architecture while carefully managing trade-offs between performance and complexity is critical for advancing these technologies. Other important considerations include guaranteeing interoperability and minimizing the burden on patients, alongside ensuring a straightforward setup, as patients cannot be expected to manage complex external sensors.[174,175]

Most existing drug delivery devices lack true remote control capabilities. While remote activation is often implemented, it usually coincides with the energy transfer and limited to triggering the actuator activation, as a matter of fact requiring the user's intervention, with all the possible consequent issues (see section 1). Only a limited number of devices, as highlighted in section 3.6, can be classified as systems with communication capabilities. Even in these

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cases, communication is typically linked to the energy transfer system. Independent communication, implemented through RF or Bluetooth technologies, remains rare. Despite demanding greater energy autonomy from the device, such communication facilitates integration with IoT systems, enabling remote patient management, increasing automation, and reducing the tasks required of patients or healthcare providers during drug administration.[174–177] Through IoT integration, implantable drug delivery systems can become nodes in a broader digital health framework, continuously exchanging data with mobile health (mHealth) platforms, clinician dashboards, or cloud-based analytics engines. This enables autonomous and continuous remote control, entirely decoupled from energy transfer sessions. It can support real-time physiological monitoring by interfacing with wearable or implantable biosensors, allowing dynamic therapy adjustment based on contextual, patient-specific data. Such infrastructure can empower clinicians to proactively manage treatment regimens, automatically trigger drug administration in response to critical biomarker changes, and receive alerts for potential anomalies or emergencies. In particular, this approach can potentially enhance patient safety by providing responses to emergencies requiring pharmacological intervention, or, in less critical scenarios, therapy adjustments tailored to the patient's physiological needs.[167,178,179]

Integration with physiological monitoring remains an open and essential topic, aligning with the development of autonomous systems for disease management. Achieving this integration necessitates either energy and communication autonomy within the system or accessibility through an external activation system. However, not all externally activated devices provide details about the size of the external control system or the potential burden on the patient. Moving the combined control and energy source externally while maintaining the internal release system may allow for miniaturization but obligates the patient to more critically rely on the correct and timely use of external instrumentation, as a matter of fact increasing the patient's burden. Nevertheless, integration with physiological monitoring aligns with the trend toward patient-specific medicine.

While these functionalities increase system complexity, they can significantly improve cost-effectiveness of care by reducing hospital access, improving adherence, and enabling early intervention. Ensuring affordability, however, requires careful balance between performance and economic sustainability of the devices. In this regard, MEMS technologies offer a key advantage: they enable miniaturization and integration of actuators, sensors, and valves within compact devices, while remaining compatible with scalable, high-precision manufacturing. Their use supports both functional sophistication and production efficiency, making them instrumental in developing accessible and clinically viable AIDDSs. The integration of sensing capabilities and connectivity with mHealth platforms opens the door to implementing artificial intelligence (AI) for autonomous and adaptive drug delivery. AI algorithms could analyze real-time data from implantable or wearable sensors – such as vital signs, metabolic markers, or behavioral patterns – to support predictive models and closed-loop control strategies. This would enable dynamic adjustment of therapy based on individual physiological needs, enhancing treatment precision while reducing patient and clinician workload. Combined with remote monitoring infrastructure, AI can facilitate early detection of deviations from therapeutic targets, optimize dosing schedules, and support the development of fully autonomous drug delivery systems, representing a key opportunity for next-generation AIDDSs within digital healthcare ecosystems. Future advancements in integrating with the biological environment and creating unobtrusive devices hinge on material selection. Flexible materials that integrate well with surrounding soft tissue while offering durability represent a promising trend compatible with electronic systems.[180] Bioresorbable electronics present significant opportunities for temporary and deeply implanted drug delivery systems, eliminating the need for explantation. However, further advancements in material science are required to develop materials whose by-products are soluble, non-toxic, and easily metabolized. Despite this, successful preliminary approaches are documented in the literature,[181–183] and these concepts have been applied to drug delivery devices.[87,99] The current bioresorbable paradigm conflicts with the integration of standard communication protocols due to the complexity required. Nonetheless, it represents a complementary and alternative paradigm.

Although these are research devices, the designs described in section 4 already are promising from a development perspective, addressing proactively emerging challenges in integration and scalability. As summarized in Table 2, these systems exemplify different engineering trade-offs and highlight both technical and regulatory barriers that must be overcome to transition from research prototypes to viable medical products. While unresolved issues remain, these designs provide a clear perspective on the challenges, allowing the implementation of iterative design processes that enabling iterative design processes that maintain the integrity of the device concept and are compatible with previous developments. By anchoring to well-defined requirements and challenges, these technologies offer greater realism, fostering innovations that could significantly impact pharmacology. The widespread adoption of systems with these characteristics would enable remote patient treatment, eliminating the need for healthcare facility visits for drug administration. This would reduce treatment costs, especially as these technologies are scaled, and improve public health outcomes. In this context, technologies advancing toward infrastructure simplification and interoperability with mHealth platforms[176,177] are particularly impactful. Systems enabling the release of pre-existing and approved drug formulations, rather than requiring reformulated drugs, present the potential advantage of a streamlined regulatory pathway. Reservoir-based systems, which do not alter the drug formulation, could expedite market access for controlled release systems by following the regulatory framework for medical devices. To date, this pathway has primarily been applied to large devices for

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Table 3 Open challenges and directions for AIDDSs

Key challenges	Future directions
Energy autonomy and miniaturization	Wireless power transfer, energy harvesting, and ultra-low-power design to reduce size and extend operational lifetime *in vivo*
Reliable and autonomous communication	Independent RF/Bluetooth communication enabling real-time, bidirectional data flow and integration with IoT/mHealth platforms for remote therapy control and monitoring
Security and privacy risks	Incorporation of secure, encrypted protocols and authentication mechanisms from early design stages to support safe remote access and data integrity
Digital health and AI integration	Leveraging AI and mHealth platforms for real-time data analysis, predictive modeling, and closed-loop control for adaptive, patient-specific drug delivery
Patient burden and usability	Development of interoperable systems with intuitive interfaces and minimal external components to reduce complexity and support user-independent operation
Manufacturability and scalability	Adoption of MEMS and microfabrication techniques for reproducible, cost-effective production at scale, while preserving performance
Validation and clinical translation	Iterative prototyping with *in vivo* testing and alignment with clinical workflows to streamline preclinical-to-clinical transition
Biocompatibility and material constraints	Use of soft, durable, and bioresorbable materials compatible with long-term tissue integration and safe biodegradation
Regulatory complexity	Streamlined approval pathways *via* use of approved drug formulations and early-stage regulatory strategy alignment
Affordability and access	Modular and scalable architectures enabling economically sustainable, intelligent systems accessible for widespread chronic disease management

end-stage diseases. However, given the advancements in miniaturization highlighted in the literature, this represents a significant opportunity for prevalent diseases. The key technological challenges and future directions to realize this potential are summarized in Table 3, offering a framework to guide further development and clinical translation.

Conclusions

The evolution of AIDDSs highlights their transformative potential to meet critical medical needs while advancing precision medicine. From the analysis conducted, several resolved issues, open challenges, opportunities, and potentialities emerge. Resolved challenges include miniaturization of actuation technologies and enhanced biocompatibility, enabling less invasive implantation and better patient comfort. Open challenges revolve around enhancing scalability, achieving true energy autonomy, and developing robust communication capabilities. Significant opportunities lie in integrating these systems within IoT frameworks, which can enable dynamic and adaptive responses not just at the timepoint of injection or implantation, but continuously throughout the therapy. These advancements will play a pivotal role in improving patient safety, particularly through real-time monitoring, emergency responsiveness, and therapy customization. To achieve this, it is foreseeable that new challenges related to security and privacy, not yet fully addressed, will emerge as remote control and communication become standard.

However, the convergence of enabling technologies – such as flexible electronics, energy-efficient powering methods, and IoT frameworks – offers a clear pathway for advancing these systems. By tackling the remaining challenges through collaborative innovation and systematic design processes, researchers and engineers can position AIDDSs as scalable, safe, and impactful tools in modern healthcare.

The AIDDS of the future must encompass a dynamic response capable of ensuring efficacy, efficiency and, most importantly, safety for the patient throughout its operation. Furthermore, it should provide adaptive and continuous care, extending beyond the moment of injection or implantation to deliver a constantly tailored response at every stage of therapy. Finally, the system should operate in alignment with the principles of precision medicine, offering real-time, patient-specific adjustments to therapy and ensuring maximum therapeutic benefit while minimizing side effects. These features will not only elevate the functionality of AIDDSs but also position them as a cornerstone of future healthcare, enabling a seamless blend of advanced technology and personalized therapeutic approaches. To fully unlock their potential, a sustained focus on real-world validation, regulatory alignment, and patient-centered design is essential. This will ensure that future systems not only achieve clinical readiness but also drive a meaningful shift toward autonomous and accessible therapeutic solutions.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analyzed as part of this review.

Author contributions

Fabiana Del Bono: conceptualization, data curation, formal analysis, investigation, visualization, writing – original draft, writing – review & editing (lead). Nicola Di Trani: writing – review & editing (equal); visualization (supporting). Danilo Demarchi: conceptualization, project administration, supervision (equal); funding acquisition, resources, writing – review & editing (supporting). Alessandro Grattoni: supervision (equal); funding

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acquisition, project administration, resources, writing – review & editing (supporting). Paolo Motto Ros: supervision (lead); conceptualization, funding acquisition, project administration, writing – review & editing (equal); resources (supporting).

Conflicts of interest

A. Grattoni is an inventor of intellectual property licensed by Continuity Biosciences. All other authors declare that they have no competing interests or consulting engagements.

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