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REVIEW ARTICLE

# Smart Drug Delivery Systems: Technological Advancements, Clinical Challenges, and Future Perspectives

Mohammad Seyedhamzeh[1], Sharareh Houshmandyar[2], Mehradad Hamidi[3,*]

[1] Zanjan Pharmaceutical Nanotechnology Research Center (ZPNRC), Zanjan University of Medical Sciences, Zanjan, Iran
[2] Department of Life Sciences, University of Bath, Bath, BA2 7AY UK
[3] Department of Pharmaceutics, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran

## ABSTRACT

Due to its technological advancements, Smart Drug Delivery Systems (SDDS) allow very high precision, exquisite control, and adaptability in drug delivery, considering spatial, temporal, and dosage parameters that are being altered intelligently by interacting with a biological cue or an external stimulus. The Systems enhance the therapeutic value of a drug while reducing the side effects on other targets and systemic toxicity. This review explains comprehensively and classifies SDDS, encompassing stimuli-responsive carriers, targeted nanoparticles actively, bioinspired cellular vectors, and device-driven platforms such as implantable pumps and wearable injectors. We explore development in nanotechnology, biomaterials, and digital health integration as well as highlighting how artificial intelligence and machine learning are facilitating the design and personalization of these systems. Regulatory landscapes and manufacturing complexities are critically discussed, alongside the socio-economic challenges affecting clinical translation and patient adherence. Emerging trends such as biodegradable materials, smart packaging, and expanding clinical applications including neurology, cardiology, and infectious disease as well as indicating a transformative era in precision medicine. Finally, we provide a looking-forward perspective which is about global market growth and interdisciplinary collaboration, underscoring the vital role SDDS will play in shaping the future of healthcare paradigms.

**KEYWORDS:** Smart Drug Delivery Systems, Targeted Drug Delivery, Stimuli-Responsive Carriers, Nanomedicine, Drug Delivery Devices, Artificial Intelligence, Nanoparticles

## HIGHLIGHTS

- Overview of the nanotechnology-based delivery carriers responsive to targeted drug delivery
- Blending AI and machine learning to tailor treatment and optimize dosing
- Bioinspired, device-enabled platforms for the creation of regulated, biocompatible drug delivery
- Clinical, regulatory, industrial, and economic problems that will be resolved through the use of SDDS

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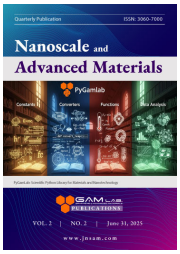


***Correspondence**
**Mehrdad Hamidi**
Department of Pharmaceutics, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran
hamidi@zums.ac.ir

List of Abbreviations

| Abbreviation | Full Form |
|---|---|
| 3D | Three-Dimensional |
| ADC | Artificial Pancreas Device / Antibody-Drug Conjugate |
| ADCs | Antibody-Drug Conjugates |
| AI | Artificial Intelligence |
| COPD | Chronic Obstructive Pulmonary Disease |
| DNA | Deoxyribonucleic Acid |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| EMA/540317/2024 | EMA Regulation Code |
| EMA/CHMP/ ICH/892561/2023 | EMA Guideline Code |
| EPR | Enhanced Permeability and Retention |
| FDA | Food and Drug Administration |
| FDA-2023-22921 | FDA Regulation Code |
| FDA-2024-N-2587 | FDA Regulation Code |
| GDPR | General Data Protection Regulation |
| GI | Gastrointestinal |
| HIPAA | Health Insurance Portability and Accountability Act |
| IDDS | Implantable Drug Delivery Systems |
| IoT | Internet of Things |
| ML | Machine Learning |
| mRNA | Messenger Ribonucleic Acid |
| NPs | Nanoparticles |
| PEG | Polyethylene Glycol |
| R&D | Research and Development |
| RNA | Ribonucleic Acid |
| SDDS | Smart Drug Delivery Systems |
| TDD | Targeted Drug Delivery |
| TRIZ | Theory of Inventive Problem Solving |

## INTRODUCTION

One of the most difficult issues in contemporary medicine is delivering therapeutic agents with maximum precision and control. Standard techniques of drug administration, like oral or systemic route injections, generally lead to the drugs scattering widely in the bloodstream thus leading to diminished drug concentration near the disease sites and unwanted adverse off-target effects. Such are attained as preventions against treatment efficiency, become toxic, and deter patients from adhering to their treatment regimen. In addressing these clinical needs, a new technological paradigm was proposed to supersede the classical drug delivery course, the so-called Smart Drug Delivery Systems (SDDS). By allowing the controlled, site-specific, and stimuli-responsive release of therapeutics, SDDS stands to redefine precision medicine by improving therapeutic indices and, simultaneously, decreasing systemic exposure(1,2).

An example of smart drug delivery can be given wherein it controls when, where, and how much drug is released, triggered mainly by biological or external stimuli. It allows spatiotemporal drug administration based on the pathophysiological state of the patient, therefore improving therapeutic outcomes and reducing side effects. The basis behind SDDS goes beyond one field name, nanotechnology, materials science, bioengineering, and molecular biology, to now include digital health technologies, AI, and ML.that not only transport drugs but also sense, respond, and adapt to the complex biological milieu(3).

Foremost in SDDS innovation sit nanoscale carriers engineered to overcome biological barriers, avoid immune clearance, and accumulate within diseased tissues. Nanomedicine approaches to smart delivery include liposomes, polymeric micelles, dendrimers, and inorganic nanoparticles, usually functionalized with targeting ligands and protective surface chemistries. These platforms operate on endogenous stimuli that include pH changes or enzymatic and redox potential activities or exogenous ones such as light, ultrasound, or magnetic field actions that induce drug release specifically at the pathological site in question. Moreover, nanoparticles and device-based delivery systems are on the rise, including implantable microchips, wearable injectors, and ingestible electronics, offering programmable, feedback-controlled drug delivery, which is matched with patient monitoring technologies(4,5).

AI- and ML-incorporated SDDS provided another dimension of personalization and autonomy. AI-driven algorithms optimize drug dosing in real-time, the data available being physiological data collected continuously, thus enabling closed-loop systems: an example is the closed-loop system similar to the so-called artificial pancreas to manage diabetes. Then, AI speeds up the rational design of drug carriers by modelling nanoparticle interactions and optimizing formulations, reducing development time and increasing efficacy levels. The interplay between computational intelligence and biomedical engineering will serve adaptive therapeutic regimens tailored to individual patient profiles and the dynamic nature of a disease state(6,7).

SDDS translation to the bedside is confronted with multi-faceted difficulties even with such encouraging developments. Designing carriers with size, shape, and payload control at nanoscale complexity as well as integrating electronics and sensing into product-based devices calls for creative scalable manufacturing techniques. Regulatory systems are changing, however, to provide answers to the particular safety and effectiveness issues of combination drug-device and nanomedicine products; nonetheless, these paths are still difficult. Ensuring biocompatibility and long-term safety calls for thorough preclinical and clinical study; unreasonably high development and deployment costs are major obstacles to commercial acceptance, especially in low-resource

environments. Patient usability and compliance are equally crucial since even the most sophisticated delivery systems are clinically only optimally effective if patients are willing to accept and use them (8,9).

Guidance frameworks have been established in the name of regulatory organisations in charge of upholding sealing to promote SDDS research and approval. These frameworks aim to standardise testing procedures for nanomaterials, combination products, and software as a medical device. Parallel efforts and increased collaboration between public and private institutions, as well as on a global scale, should speed innovation and provide a more suitable climate for SDDS commercialisation. Another illustration of the translational power of collaborative research and regulatory agility in supporting smart delivery technology is the rapid launch of lipid nanoparticle-based mRNA vaccines during the COVID-19 pandemic(10–12).

The SDDS has indeed grown to include neurology, cardiology, autoimmune disorders, and chronic diseases. New bioinspired delivery techniques confer unmatched target selectivity and immunocompatibility by employing endogenous biological carriers such as exosomes and modified cells. At the same time, advances in biodegradable and biointegrated materials are set to usher in a new era for implantable devices that dissolve post-therapeutic action, hence minimising the long-term hazards and their impact on the environment(13).

The review period discovered and summarised the ten years of advancement in smart drug delivery systems (2015-2025) covering foundational definitions, classification methods, supporting technologies, clinical applications, regulatory perspectives, and prospective directions. It casts a critical eye over landmark breakthroughs in nanotechnology, implantable and wearable devices, integration with AI, and bioinspired platforms-auditing achievements along with lingering challenges. We also analyze the socioeconomics and ethics that should be considered in the smart development and deployment of SDDS. Lastly, an optimistic trajectory of the field in light of trends and worldwide markets will give researchers, clinicians, and policymakers insight into the transformative capabilities of smart drug delivery within precision medicine.

In the subsequent sections, we will start by giving a more precise definition and regulatory context for SDDS. This will be followed by the delineation of major classes of systems largely depending on mechanisms and design. We will then have a section on state-of-the-art technology, emphasizing the areas of nanomedicine, device-based platforms, and AI-enabled personalization. The existing bottlenecks in manufacturing, safety, regulatory approval, economics, and, finally, patient-centred acceptance will then be treated. The review will conclude with a discussion of emerging trends in biodegradable materials, smart packaging, and expanding therapeutic indications that will shape the future of SDDS. The entire review is offered to emphasize the multidisciplinary nature of smart drug delivery and the importance that it holds in the transformation into an era of safer, more effective, and personalized treatments.

## 1. DEFINITION OF SMART DRUG DELIVERY SYSTEMS

Smart drug delivery systems (SDDS) refer to advanced methods or technologies that transport therapeutic agents in a controlled, targeted, and intelligent manner to achieve improved treatment outcomes. Unlike conventional drug delivery (where drugs disperse non-specifically in the body), an SDDS is designed to deliver medication to specific sites at the right time and dose, often responding to feedback or stimuli(14,15). In other words, these systems "smartly" adjust when, where, and how a drug is released for example by sensing a trigger (like pH or temperature) or by recognizing a target tissue to maximize efficacy and minimize side effects(16,17). Targeted drug delivery is often used synonymously with smart drug delivery(18), emphasizing that the drug is delivered intelligently to a specific organ, cell type, or even intracellular compartment rather than diffusing throughout the body. Overall, a smart drug delivery system aims to optimize therapeutic effect (by concentrating the drug at the site of need) and reduce toxicity (by sparing healthy tissues), thus improving patient outcomes and adherence(19). Key features that frequently characterize SDDS include on-demand or feedback-regulated drug release, pre-programmed release profiles, stimuli-responsiveness, and spatial targeting ability(20).

Despite the widespread use of the term "smart drug delivery" in academia, there is no single formal regulatory definition dedicated to SDDS. Regulators like the U.S. FDA and EMA typically discuss such technologies under broader categories (e.g. targeted drug delivery, controlled-release formulations, or nanomedicine products) rather than using the label "smart"(21,22). In academic literature, however, the definition of SDDS is relatively consistent and well-accepted. Generally, it refers to stimuli-responsive or targeted drug delivery systems that adjust drug release rates or localization in response to specific conditions(23). For instance, a recent review defines Smart Drug Delivery Systems as "stimuli-responsive [systems] that can be modified in chemical structure in response to light, pH, redox, magnetic fields, [enzymes], etc."(24). This aligns with other scholarly definitions highlighting that an SDDS should deliver drugs "at the correct time with an exact dose... with efficiency and specificity to the targeted cells," often by exploiting biological cues or external triggers(17,25).

From a regulatory perspective, agencies focus on the functional capabilities and safety of these systems. For example, the FDA considers many smart delivery products as nanomaterial-containing drug products or combination products and emphasizes that they must meet the same safety and efficacy standards as traditional drugs while managing

**Table1 |** Comparative Regulatory Requirements for Advanced SDDS (2023-2024 Standards)

| Parameter | FDA Requirements (21 CFR 4.3) | EMA Requirements (Annex XIV) | Harmonization Status (ICH) |
|---|---|---|---|
| AI Algorithm Validation | • 3-month clinical drift testing<br>• Bias mitigation documentation<br>• Fail-safe protocols for connectivity loss | • 6-month simulated use validation<br>• Training dataset diversity audit<br>• Real-world performance monitoring | • Q14 Working Group (2025 target)<br>• Partial alignment on drift thresholds |
| Nanoparticle Characterization | • DLS size distribution ±10%<br>• Zeta potential ±5 mV batch consistency<br>• 90% drug loading efficiency | • TEM validation + ELS<br>• Surface ligand density quantification<br>• 95% encapsulation efficiency | • Partially aligned (Q12 draft)<br>• Size standards harmonized |
| Biodegradation Testing | • 6-month mass loss data<br>• GLP toxicology of degradation products<br>• Environmental impact assessment (≥5% concentration) | • 12-month byproduct toxicity<br>• Enzymatic degradation profiling<br>• Ecotoxicity screening (OECD 201) | • Discrepancy under review<br>• ICH environmental working group formed |
| Wireless Connectivity | • FCC Part 15B compliance<br>• ISO 13485:2023 cybersecurity<br>• 99.9% data transmission reliability | • RED Directive 2024/53/EU<br>• GDPR-compliant data encryption<br>• Electromagnetic compatibility testing | • Mutual recognition in progress<br>• IEC 80601-2-71 alignment |
| Real-World Evidence | • 500-patient-year post-market data<br>• Continuous glucose monitor integration<br>• PRO collection via mobile platforms | • 300-patient prospective registry<br>• Sensor accuracy validation<br>• Linked electronic health records | • ICH RWE Framework (2024) adopted<br>• Common endpoints established |

any unique risks(26). (Notably, the FDA's 2022 guidance on nanomaterial-containing drugs explicitly states the agency does not prejudge nanoscale products as inherently benign or harmful but requires appropriate risk assessment and data.) The European Medicines Agency (EMA) has issued a series of Reflection Papers to guide the development of nanotechnology-based medicines – covering topics like liposomes, polymeric micelles, and surface-coated nanoparticles – thereby creating de facto standardized expectations for smart delivery systems in the EUgabi-journal.net. Academically, a "smart" delivery system is also expected to fulfil certain criteria: e.g. protect the drug from premature degradation, cross biological barriers to reach the target, release the drug in a controlled dose at the target site, and ideally self-regulate according to feedback (a classic example being glucose-responsive insulin delivery for diabetes)(27–29).

Advances in Smart Drug Delivery System (SDDS) technologies and, more particularly, artificial intelligence and implantable devices have shifted shifts in worldwide regulations. In the US, FDA's 2023-2024 regulatory update for AI/ML-based medical devices (FDA-2023-22921) classifies autonomous dosing algorithms as legally Class II medical devices, hence making them subject to more regulation. Such classification involves meeting three basic requirements: (1) regular performance monitoring procedures to ensure algorithmic efficiency and safety in the long run; (2) precise recording of safeguards against bias to audit deviation in AI-based dosing decisions; and (3) fail-safe mode functionality to provide operational integrity in the long run on communication failure.

Parallel to this, the European Medicines Agency (EMA) has released the 2024 Guideline on Implantable Drug-Device Combinations (EMA/CHMP/ICH/892561/2023), which pronounces a tiered biocompatibility test strategy risk-proportional and device implantation time-dependent. Permanent devices, in the new paradigm, need 12-month degradation and incorporation testing, whereas biodegradable systems have safety evaluation in 6 months and are an even more risk-proportional regulatory approach (Table 1).

Notably, the two authorities have also enhanced environmental regulation. As discussed in FDA-2024-N-2587 and EMA/540317/2024, ecotoxicological risk assessment is mandatory for nanocarrier-based systems with a concentration of over 5% by weight of active pharmaceutical ingredient, implying heightened regulatory concern with the environmental impacts of nanomedicine(30–32).

## 2. CLASSIFICATION OF SMART DRUG DELIVERY SYSTEMS

Smart drug delivery systems can be classified in several ways. Figure 1 displays five types of drug delivery systems targeting the future of targeted therapy. Stimuli-responsive systems are defined as those that operate with the release of a drug resulting from some external or internal stimulus, e.g., a pH, temperature, or light-initiated change, thus granting some control over where and when the drug will act. Active targeting systems achieve treatment selectivity, recognizing specific cells with antibodies or ligands and binding onto them, thereby causing maximum off-targeting and side effects. Such nano-carriers of the usual size of 1 to 200 nanometers work for the controlled and stealth release of the therapeutic entity across biological barriers with

little or no degradation, retention, or clearance in the biological pathway en route to the region of interest. Smart drug delivery uses programmable electronic implantable devices and wearable systems that permit real-time monitoring and controlled dosing of therapeutics toward final personalized medicine. Lastly, bioinspired and cellular drug delivery systems tap into nature's biological transporters like exosomes and engineered cells to attain productive drug delivery that is highly biocompatible and targeted. Together, these novel delivery systems constitute the next generation of therapeutics that will improve drug delivery's safety, efficacy, and patient amenability. Below is an overview of the main categories of SDDS, organized by mechanism and design approach:

Stimuli-Responsive Delivery Systems: These systems (sometimes called "environment-responsive" or "triggered" delivery) release their drug payload in response to specific stimuli. The trigger can be internal physiological cues – such as pH variations, enzymatic activity, redox conditions, or temperature differences in certain tissues – or external stimuli applied by clinicians, such as light, ultrasound, magnetic fields, or electric pulses (33,34) For example, a pH-sensitive polymer nanoparticle can remain intact in the bloodstream (neutral pH) but rapidly release the drug upon reaching an acidic tumour microenvironment or endosome (lower pH). Similarly, magnetic nanoparticles can be guided to a location with an external magnet and heated (magnetothermal effect) to trigger drug release on-site. Stimuli-responsive systems add a layer of "smartness" by ensuring drug release happens preferentially at the target site or timing of interest. This class includes pH-responsive hydrogels, thermosensitive liposomes, ultrasound-triggerable microbubbles, and other tunable materials(35). Many experimental SDDS in the past decade have focused on designing novel stimuli-responsive carriers (for instance, nanocarriers that only release chemotherapy drugs in the higher enzyme concentrations found in tumours, or insulin depots that automatically release insulin when glucose levels rise). The goal is a self-regulated therapy, improving safety and efficacy by on-demand drug release coupled with real-time conditions(36).

Actively Targeted Delivery Systems: These smart systems are engineered to home in on specific cells or tissues using molecular recognition. Often termed "targeted drug delivery" (a subset of SDDS), they employ targeting moieties such as antibodies, peptides, aptamers, or other ligands attached to a drug carrier that bind selectively to receptors overexpressed on the diseased tissue(37). For example, a nanoparticle can be coated with folic acid to target folate receptors on cancer cells(38), or with an antibody that recognizes an antigen on tumour or inflammatory cells. Once injected, such a carrier actively seeks out the target via biochemical interactions (as opposed to passive accumulation alone). Active targeting is often combined with nanocarriers (see next category) and can achieve higher local drug concentrations in the intended tissue while reducing off-target effects(39). Another form of targeting is "organotropism" designing carriers that naturally accumulate in certain organs (for instance, using cationic carriers that cross the negatively charged glomerular membrane for kidney targeting, or using transferrin-modified particles to cross the blood-brain barrier)(40). Passive targeting (not truly "active" but often discussed in this context) relies on natural biodistribution advantages e.g. the Enhanced Permeability and

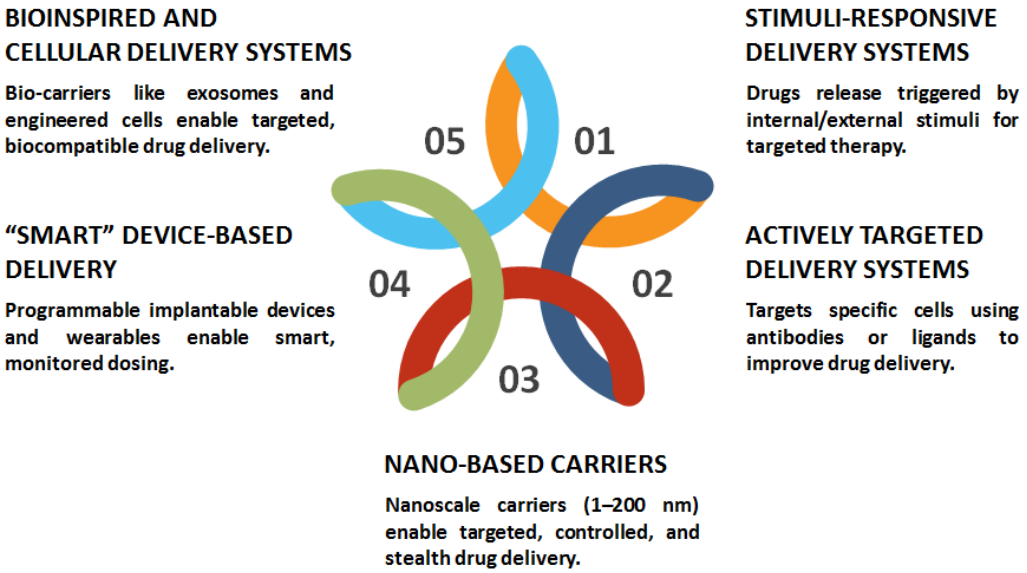


**Figure 1** | Classification of Smart Drug Delivery Systems (SDDS)

Retention (EPR) effect in tumours allows nanosized particles to accumulate in tumour tissue due to leaky vasculature(41). All FDA-approved cancer nanomedicines to date rely on this passive targeting via EPR(42). Smart targeted systems aim to refine this further, by adding active homing mechanisms or triggerable release at the target, thereby delivering the drug specifically to the disease site (tumour, infected organ, etc.) and ideally even into the target cells (e.g. via ligand-mediated endocytosis)(43).

Nano-Based Carriers (Nanomedicine Systems): A large proportion of smart delivery systems are nanoscale carriers – typically in the 1–200 nm size range – which confer unique delivery capabilities. These nanocarriers include lipid-based nanoparticles (liposomes, solid lipid nanoparticles, lipid–polymer hybrids, lipid emulsions), polymer-based nanoparticles (biodegradable polymeric NPs, polymer micelles, dendrimers, nanogels), inorganic nanoparticles (such as iron oxide nanospheres, gold nanoparticles, silica nanoshells, quantum dots), and even biomimetic nanocarriers like exosomes or cell-membrane-coated nanoparticles(44,45). Nanoparticles are considered "smart" because their size and surface can be engineered to navigate biological barriers and release drugs in controlled ways. For instance, polymeric micelles (~20–100 nm) can solubilize hydrophobic drugs in their core and release them slowly, extending the drug's half-life. Liposomes (50–150 nm vesicles) can carry drugs and release them when the liposome is destabilized by an environmental trigger (pH or temperature-sensitive liposomes exist that release contents when heated or in acidic environments). Figure 1 below illustrates the major classes of nanoparticle carriers and their typical advantages/disadvantages. Nano-based systems are central to smart delivery because they can be functionalized (e.g. with targeting ligands, stealth coatings like PEG to evade the immune system(46)), and can be made stimuli-responsive (e.g. gold nanoshells that heat up with infrared light to trigger drug release). They also excel at improving pharmacokinetics – nanoparticles can prolong circulation time, protect drugs from degradation, and preferentially accumulate in certain tissues. Over the last 10 years, nano-drug delivery has been the dominant paradigm in smart delivery research and product development, yielding most of the clinical successes.

"Smart" Device-Based Delivery: Not all smart delivery systems are nanoparticles or chemical formulations; some are device-driven or electronic systems that intelligently control drug administration(47). These include implants and microchips that release drugs on a programmed schedule or via remote control, micro infusion pumps (such as insulin pumps that adjust doses based on glucose sensor feedback), and ingestible electronic pills. For example, researchers have developed implantable microchip-based reservoirs that can be triggered wirelessly to release precise drug doses at specific times – a smart replacement for periodic injections(48). Another growing area (in the past decade) is "smart pills" with integrated sensors or electronics(49): one FDA-approved example is a pill for schizophrenia that contains an ingestible sensor transmitting data when the pill is taken, thus tracking adherence. While that particular example is about monitoring, other smart pills under development can respond to GI tract conditions (e.g. release drug only upon reaching the colon by sensing gut pH) or can be triggered by an external signal (for on-demand drug release in the GI tract). Smart inhalers and smart injectors have also emerged – these combine traditional drug devices (inhalers, epinephrine pens, etc.) with sensors, Bluetooth connectivity, and dosage-control electronics to optimize delivery and improve patient use. In summary, this category transforms drug delivery from purely biochemical release mechanisms to electromechanical control systems, leveraging the Internet of Things (IoT) and wearable tech (50). These devices may not "target" a particular tissue in the molecular sense, but they optimize timing, dosing, and monitoring, which is an important aspect of smart delivery (especially for chronic conditions). For instance, next-generation insulin pens and inhalers now record dosing events, provide patient reminders, and adjust dosing based on patient input – effectively creating a smarter delivery regime(51).

Bioinspired and Cellular Delivery Systems: An emerging class of SDDS involves using biological carriers or constructs to deliver drugs. These include exosome-based drug delivery (using or mimicking the body's cell-derived vesicles for targeted transport) and cell-mediated delivery, where cells like engineered T-cells, macrophages, or platelets ferry drug-loaded nanoparticles to a target (taking advantage of cells' homing abilities)(52,53). Exosomes have gained attention in the last 10 years as natural "smart" nanocarriers – they are biocompatible, have inherent targeting to parent cell types, and can cross biological barriers; for example, researchers suggest exosomes could serve as non-immunogenic nanocarriers that naturally target certain tissues(54,55). Another bioinspired approach is bio-responsive polymer conjugates – drugs attached to polymers or antibodies that activate only in the disease microenvironment (e.g. antibody-drug conjugates (ADCs) which release a cytotoxic drug inside target cancer cells)(56).

## 3. EMERGING TECHNOLOGIES IN SMART DRUG DELIVERY

Recent advancements in technology have significantly enhanced the precision, responsiveness, and patient-centricity of drug delivery systems. Figure 2 illustrates four paramount emerging technologies ushering in change in the drug delivery arena. First, nanocarriers are designed to be responsive to stimulation, thus the degranulation of drugs and helping target and treat various diseases to a greater extent. Secondly, implantable pumps and smart pills administer therapies continuously in an individualized manner while maintaining close monitoring of medication so that drug administration

can be reasonably precise. Third, the wearable injector and smart inhaler use Bluetooth to dose, monitor, and control treatments in real-time, thus promoting the patients' autonomy in treatment management. Lastly, AI and machine learning algorithms serve to optimally plan drug design, dosing schedules, personalization, and predictive care for better therapeutic outcomes and more efficient clinical trials. These innovations are at the forefront of transforming truly patient-centric drug delivery into smart drug delivery, safer drug delivery, and responsive drug delivery solutions. Key innovations in this space include the development of nanotechnology-based carriers, bio-responsive materials, implantable and wearable devices, and the integration of digital technologies with artificial intelligence (AI). Below, we explore these emerging technologies and their impact on smart drug delivery(57).

### 3.1 Nanotechnology and Stimuli-Responsive Carriers

Nanotechnology has developed a number of different types of nanocarriers that can carry drugs, depending on the substance. There are several materials that can be used for this, such as bare polymeric nanoparticles, liposomes, micelles, dendrimers, metal or silica nanoparticles, and more(58). One thing that sets these nanoparticle systems apart is that they may respond to stimuli from outside or inside the body, which makes it possible to control or release medication as needed. For instance, nanoparticles may be inactive while they are circulating, but they can release their pharmacological payload when they come into contact with acidic pH (tumor tissues), enzymes, temperature, light, or magnetic fields. Because of this, these bio-responsive devices only administer drugs to a certain place or set of conditions, so healthy tissues don't get hurt in the process(59).

Nanocarriers linked to tumor-specific ligands like antibodies or peptides can, for example, target cancer cells specifically and release chemotherapy drugs in reaction to the tumor microenvironment. This two-step targeted method—ligand recognition and stimulus-responsive release makes the treatment much better(60). But sophisticated delivery methods based on nanotechnology aren't just for cancer. Stimuli-responsive carriers, such polymers and hydrogels, can also be used to treat diabetes (for example, releasing insulin from a hydrogel when glucose levels are high) and autoimmune illnesses. Nanocarriers made of organic materials

### 3.2 Implantable and Ingestible Drug Delivery Devices

Implantable drug delivery systems (IDDS) are one of the recent innovations in drug delivery technology. IDDS are introduced into the body and deliver long-term, tailored treatment. IDDS include implantable infusion pumps to deliver drugs like painkillers, insulin, or chemotherapy at a pre-set rate and drug-eluting stents to release drugs into the walls of blood vessels(61).

For example, implantable pumps with sensors are utilized to administer precise doses of insulin or pain medication on the basis of sensor feedback in real-time. This maintains blood glucose and pain levels reasonably stable. Microchips, or tiny reservoirs to be refilled and regulated remotely, are another form of popular implant(48). Researchers have demonstrated that chemotherapeutic drugs may be held in reusable reservoirs by an implantable micropump that is wirelessly powered. The method has the promise of releasing doses on demand, inhibiting tumor cell growth in vitro, demonstrating the principle of "on-demand" therapy. The implant sits idle or dispenses medicine only when instructed to by a physician or an automated system. It may therefore facilitate more targeted treatment to the patient's individual needs(62). Another innovation is ingestible

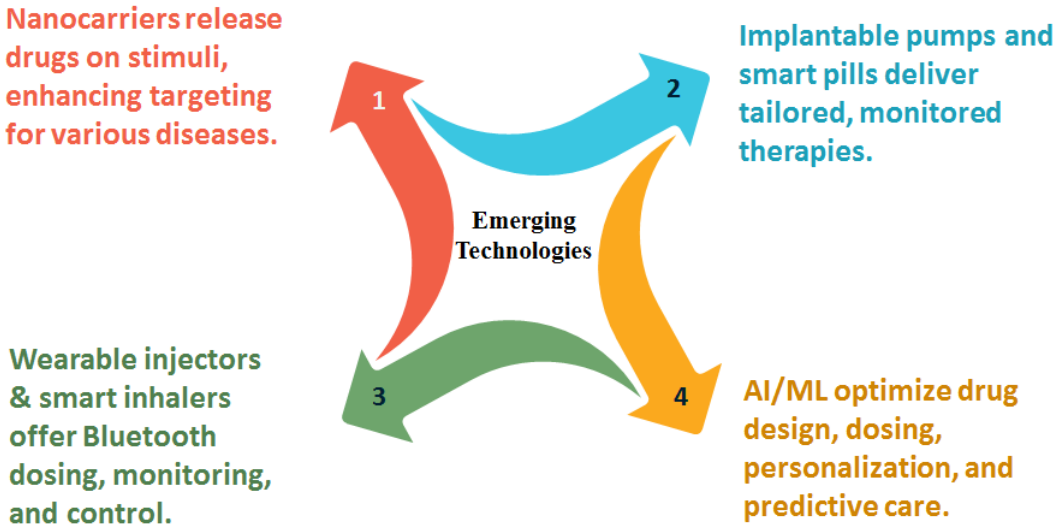


**Figure 2** | Emerging technologies in Smart Drug Delivery Systems

smart tablets, which are tablet-sized pieces of equipment that can perform some of their duties in the GI tract.

Some are designed to diagnose an illness or administer drug at some specific site in the GI tract. For example, a tablet that contains an ingestible sensor and has been cleared by the FDA sends a message to a smart phone app or to a wearable patch as it dissolves in the stomach. This ensures the tablet was taken and tracks compliance. In addition, some food items can electronically control the drug delivery in the intestine or address a section of the intestine for local administration. These emerging concepts have much potential, especially for conditions that require rigid compliance or ongoing therapy, such as hormone deficiency, epilepsy, and pain(63).

### 3.3 Wearable Drug Delivery Platforms and Connected Devices

Wearable drug delivery systems transform the management of chronic therapy, with enriched convenience and connectivity to the patient. On-body infusers and patch pumps for insulin and biologic drugs already exist; these attachments stay on the skin and can be set to deliver medications subcutaneously at scheduled times or through patient activation. For example, the on-body injector Vertiva, set to hit the markets in 2024, can hold 10 mL of high-viscosity biologic therapeutics. It can be programmed for multiple dosing regimens, from a continuous micro-dosing administration profile to a complete bolus injection administration profile. Conveniences include injectors suitable for large-volume or high-viscosity drugs, such as monoclonal antibodies, which would require cumbersome delivery administration through a single-dose syringe. With miniaturized motors or piezoelectric pumps, wearable injectors provide doses over time without requiring the patient to handle a syringe, thus improving comfort and compliance(64).

Other wearable devices are smart inhalers. These are for exercise-induced respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD). Smart inhalers have sensors and Bluetooth, and use is registered automatically, time-stamped, and dated with each dosage. This information can be sent to a smartphone application or cloud platform for physicians to access and monitor usage. Smart inhalers ensure appropriate and consistent medication use. For instance, in children with asthma, sensor-enabled inhaler caps significantly improved medication use and symptom control, which reassured caregivers. More than respiratory drugs, networked intranasal drug delivery devices are currently being studied in neurological conditions, such as Parkinson's and Alzheimer's, because intranasal delivery can bypass the blood-brain barrier. Such devices might adapt therapy in real time in response to patient feedback, providing accurate and adaptive treatment(65).

Other innovations in diabetes management occur when smart pens are worn on the body. Smart insulin pens or pen add-on caps monitor doses and timing of insulin, sometimes in conjunction with a mobile app to help patients and physicians optimize insulin treatment. For instance, Medtronic's InPen and other connected pens have real-time dosing calculators and insulin monitoring capabilities, providing better management of insulin delivery(66). The later 2024 revision of the intelligent pen system was FDA-approved, incorporating continuous glucose monitor data to allow the strategy of a closed-loop "artificial pancreas"(67,68).

What sits at the core of the operation of these wearable devices is connectivity and real-time monitoring. Typically, these devices leverage Bluetooth or IoT to connect to a companion app or hospital system to inform therapy via data. For example, an innovative infusion pump in the hospital can alarm or modify dosing based on an identified anomaly, all automatic entries into the electronic health record. Similarly, injector wear of a patient could upload usage data to their clinic, allowing remote monitoring of treatment response and adherence. Merging wearable technology with digital health platforms makes drug delivery an integrated part of connected care(69).

### 3.4 Artificial Intelligence and Smart Drug Delivery

AI is used ever more in designing and operating smart drug delivery systems. Researchers are employing machine learning software to determine the optimal drug-carrier compositions and forecast how changes to the design of nanoparticles might influence drug distribution and action. For example, AI nanoparticles can change their surface properties in real-time or target them specifically to particular disease locations, directing the drug carriers to the desired sites. Even though theoretical, the combination of AI and nanomedicine has the potential for highly responsive drug delivery platforms that could adjust their behavior based on patient-specific information or treatment feedback(70).

More explicitly, machine learning and AI are also being employed to optimize dosing and timing of treatment in networked delivery devices. A prime example is the closed-loop insulin delivery system, also popularly called the "artificial pancreas," which uses algorithms to scan continuous glucose monitor data and automatically adjust insulin infusion rates. Such algorithms increasingly use machine learning to improve their accuracy and personalization with time. In broader applications, AI may search enormous amounts of data from smart wearables, pumps, and inhalers to identify patterns, such as anticipating that a patient is likely to miss a dose, triggering an intervention, or anticipating disease flares in advance based on imperceptible trends. A recent advancement combined IoT sensors with machine learning algorithms to predict insulin dosing needs in people with diabetes, allowing remote adjustment without repeated clinic visits(71).

AI is also improving significantly in clinical trials of new drug delivery technologies. AI can map patient compliance against clinical outcomes by analyzing sensor data from clinical trials, providing insightful information on how different

drug delivery devices function. Pharma companies are also increasingly collaborating with technology partners to infuse drug delivery devices with AI capabilities, such as more innovative dose reminders, voice-activated injectors, and refill predictions. Hospitals also deploy AI-aided infusion systems that cross-check doses against patient vitals and medical history in real time, minimizing errors. Overall, AI enhances the "smart" in smart drug delivery, making systems more autonomous, personalized, and capable of learning from each patient's data to optimize therapy(72,73).

## 4. CHALLENGES FOR SMART DRUG DELIVERY SYSTEMS

Despite their potential advantages, smart drug delivery systems (SDDS) face challenges that must be surmounted before they can see extensive use and realize their full effectiveness in clinical practice. These challenges span material science, engineering, clinical practice, regulatory, and economic domains. The most significant issues to be tackled are as follows:

### 4.1. Biocompatibility and Safety

Advanced drug devices and carriers must be biocompatible to perform their functions as required without causing adverse immune reactions or toxicity. Specific nanomaterials, such as certain polymers, metals such as silver and gold, and carbon nanotubes, have demonstrated toxic or immunogenic effects in biological systems. For example, although carbon nanotubes can efficiently deliver drugs or genes, it has been feared they exert harmful effects on organs such as the lungs, liver, kidneys, and the immune system. Thorough preclinical experiments must ensure their safety. Furthermore, the body's natural defenses, specifically the liver and spleen mononuclear phagocyte system, may recognize nanoparticles as foreign and eliminate them, reducing their efficacy and potentially leading to accumulation in detoxifying organs(74,75).

This biocompatibility issue extends to device implants as well. Implant materials must not cause chronic inflammation, fibrosis, or immune rejection. The trade-off between function and biocompatibility is a challenging issue, and therefore, researchers are exploring biodegradable materials that get resorbed after delivering the drug. Biomimetic coatings, such as mimicking cell membranes, are also being explored to help nanoparticles evade immune detection(76).

### 4.2. Manufacturing Complexity

The fabrication of intelligent drug delivery systems is typically more complex than traditional drug delivery systems due to the inclusion of sophisticated carriers, electronics, and even sensors. For instance, the fabrication of stable nanoparticles of specific size and drug loading is far more complex than the fabrication of traditional pills. The fabrication of implantable microdevices also requires both pharmaceutical and microelectronics fabrication, which are two distinct processes and must be ideally integrated(77).

Quality control and consistency on a large scale are complicated to maintain. Slight formulation changes can change the nanoparticle's behaviour and efficacy. Some of the newer delivery modalities also require sterile assembly of electronic components and drug reservoirs, which requires new manufacturing paradigms. Automation is also tricky when materials are delicate or procedures are untried. These problems add to the expense of production and can slow down the process from prototype to large-scale manufacturing. The discipline is ongoing in addressing solutions, such as 3D printing of complex drug delivery devices, modular manufacturing of combination products, and scale-up methods for nanocarriers(78,79).

### 4.3. Regulatory and Approval Challenges

One of the biggest SDDS challenges is navigating regulatory pathways. These products often require the integration of drug, device, and sometimes biologic characteristics, making their approval complex. Regulating agencies like the FDA and EMA have combination product pathways in place. Still, the approval is time-consuming and requires demonstration of safety and efficacy for both drug and device parts. Proving the reliability of any electronics or software components of the delivery system can prove challenging, such as the need to ensure that devices will function as planned throughout their use(80).

Regulatory guidance for novel systems, such as AI algorithms that adjust dosing (which are treated as software as a medical device) or ingested pill sensors, is still evolving. Also, with the increase in connected devices, other regulatory considerations exist, including ensuring cybersecurity and data privacy, as the devices can be hacked or experience data breaches. Adhering to requirements in multiple spaces (pharmaceutical Good Manufacturing Practices, medical device quality systems, software validation, and cybersecurity requirements) is highly expected. These hurdles can slow down development timelines and require interdisciplinary regulatory affairs experience. However, regulatory bodies are trying to give more precise guidance, such as the FDA's Digital Health Innovation Action Plan, which is operating to clear the approval pathway for new therapies(81).

### 4.4. Prohibitive Costs and Economic Viability

Smart drug delivery systems are costly to design and execute. Iterative R&D is required to create such complex systems, and the manufacturing processes are expensive. Accordingly, many SDDS products are pricey, and their cost-effectiveness and economic viability are a concern. For example, advanced wearable injectors or closed-loop pumps can cost hundreds to thousands of dollars, which can be a significant barrier to healthcare systems and patients' adoption on a large scale, particularly in resource-scarce settings(35).

A recent analysis highlighted that the high development, manufacturing, and adoption costs are a significant barrier

to industry entry in the SDDS market. To justify these costs, these systems must demonstrate clear improvement in patient outcomes or generate savings, for instance, by preventing hospitalization through improved disease control. An additional financial challenge includes reimbursement, as insurers must decide whether to cover these devices and under what conditions. Without insurance reimbursement, patient adoption will be hindered. As technologies mature with time and production scales are ramped up, the unit costs should decrease. However, demonstrating cost-effectiveness remains an essential barrier to commercialization. Developers are recommended to incorporate cost modeling into development at an early stage and think about value-based pricing or health economic studies to support the financial viability of products(27,82).

### 4.5. Patient Adoption and Adherence

One of the primary motivations for SDDS is to help improve patient adherence to prescribed therapies. Yet such systems can only be successful if patients are willing and capable of using them correctly. Usability is a top priority. Patients may abandon the device if a wearable injector is cumbersome or uncomfortable, or a smart inhaler is too difficult to link with a mobile phone. Human factors are also at play some patients are uncomfortable with technology or will neglect to charge a device.(83)

Historically, roughly 50–60% of chronically ill patients have failed to take their medications as instructed, and non-adherence has been estimated to cause nearly 69% of medication-related hospitalizations. Smart devices aim to reduce forgetfulness through automation of dosing or reminding the patient, but also introduce novel adherence challenges, such as device maintenance. Patients have been found in clinical trials to have the same adherence issues with devices as they do with pills. To mitigate this, developers simplify user interfaces, provide training, and offer ongoing support. For example, some wearable injectors are designed to start automatically on application, minimizing user error. Patient acceptance studies also emphasize the importance of physical and psychological comfort in incorporating electronics or implants in treatment. Lastly, optimizing patient compliance with smart drug delivery systems requires patient-focused design and education so that such systems are viewed as a benefit and not a burden(84).

### 4.6. Integration with Digital Infrastructure

As intelligent delivery devices generate data and interact with health IT systems, the challenge lies in delivering interoperability, data security, and privacy. Providers want seamless data integration from smart pumps or inhalers into electronic health records (EHRs), but different devices may be on various platforms and standards, and integration may be complex. Standard protocols are necessary so that information from devices, e.g., an oncology drug implant, can be viewed alongside lab results within the hospital system(85).

Data security is another concern since IoT-enabled drug delivery systems must guard against unauthorized access. A breach could reveal sensitive health data and potentially allow malicious control of a device. A 2023 review identified data security, privacy, and reliability as significant challenges facing IoT-based drug delivery systems. It is also essential to ensure compliance with HIPAA and GDPR standards because such devices typically transmit private health data. Most companies use robust encryption, cybersecurity testing, and compliance frameworks to mitigate these challenges(86–88).

As more hospitals and healthcare providers adopt these technologies, integration with existing infrastructure is also of prime importance. Healthcare providers must also ensure that their networks support these devices interference-free, for which they must update their Wi-Fi and Bluetooth configurations. Overcoming these integration and data security issues is a daunting task. Still, the efforts are already underway, and many hospitals are integrating AI and predictive models with their EHR systems to facilitate intelligent drug delivery(89,90).

## 5. FUTURE TRENDS AND OUTLOOK

Smart drug delivery systems (SDDS) will remain increasingly personalized, smart, and at the center of healthcare. Several emerging trends are expected to shape the industry's future landscape, promoting innovation and improving patient care. Figure 3 depicts the major trends of the future that will shape the development of SDDS. They are moving toward an integrated, smart, and personalized view of healthcare. Precision and personalized medicine will be based on treatment linked with patients' genomic information and real-time capturing patients. Second, AI and ML convergence will be employed to enable adaptive control, predictive maintenance, and patient assistance for making devices intelligent and autonomous. Third, biodegradable and biointegrated devices will improve safety and sustainability by the capability of devices to degrade innocuously or be integrated with body tissue. Fourth, compliance technology and smart packaging will improve medication adherence through electronic and sensor monitoring. Fifth, the therapeutic and clinical uses of SDDS will be extended to neurological, cardiovascular, infectious, and surgical indications with state-of-the-art diagnostics and treatments. Lastly, SDDS are on the verge of realizing a gigantic increase in their global market size on the momentum of technological advances and increasing demand for accurate healthcare worldwide. The following are the key trends expected to define the development of SDDS in the coming years.

### 5.1. Precision and Personalized Medicine

Smart drug delivery systems will also facilitate the trend toward precision medicine by delivering treatments tailored to an individual patient's profile. Such tailoring involves adjusting drug doses, timing, and targeting based on a patient's genetics, disease biomarkers, or real-time physiological feedback.

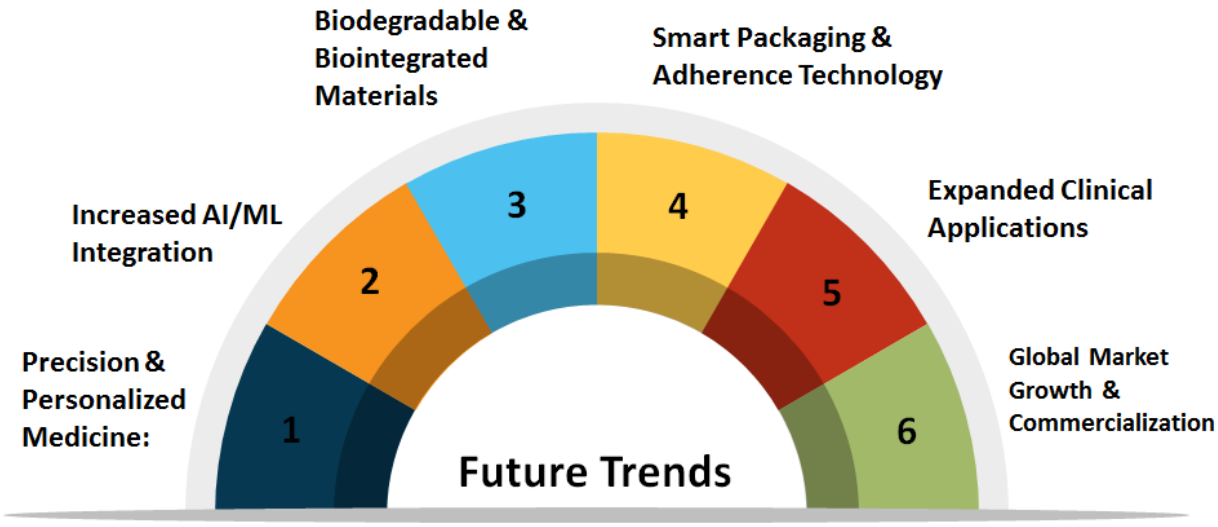


**Figure 3** | Key future trends shaping the evolution of Smart Drug Delivery Systems

Implantable pumps, for example, will soon be able to utilize patient-specific algorithms that learn from each patient's data to personalize dosing for Parkinson's drugs or chemotherapy. Nanocarriers are also being engineered to deliver drug cocktails tailored to a patient's tumour genetic profile. The ultimate goal is to create fully personalized drug delivery systems, where each patient is given a customized treatment regimen that includes the best drug at the best dose and time. Omics technology (e.g., genomics and proteomics) and diagnostic biomarker development will continue to enhance these systems, enabling more innovative and more effective therapies. Clinical trials are already underway that investigate the use of smart injectors and inhalers to individualize treatment based on patient phenotype or biomarker levels, as opposed to the conventional one-size-fits-all dosing approaches(91).

### 5.2. Increased AI/ML Integration

Artificial intelligence (AI) and machine learning (ML) within drug delivery systems will expand, presenting new opportunities for adaptive control and autonomy of systems. Future SDDS will utilize AI and ML for real-time adaptation, creating a closed feedback loop where the device learns and improves over time. For instance, AI algorithms can predict an asthma attack from a patient's usage patterns and automatically adjust the dose of inhaled anti-inflammatories. AI and ML will also be utilized for predictive maintenance of devices, alerting users when a pump will most likely fail or when a battery is running low. Additionally, these technologies can help in patient assistance through virtual assistants that guide patients on properly using their devices. On the R&D side, AI will continue to enable drug formulation advancements by predicting the optimal nanoparticle to deliver a specific drug after analyzing the big data of possible candidates. AI-powered nanorobotics, like AI-guided nanorobots navigating the body, is another promising possibility explored in preliminary research. Overall, AI and ML will improve the autonomy, safety, and personalization of SDDS treatments, making them more responsive and tailored to individuals(92,93).

### 5.3. Biodegradable and Biointegrated Materials

A recent trend in SDDS is the development of biodegradable and bio-integrated materials for carriers and delivery devices. This shift aims to address long-term safety concerns, such as the need for surgical removal of implants, and lower the environmental impact of medical devices. Research has been focused on creating nanomaterials that naturally degrade into non-toxic products after delivering their drug cargo. This improves patient safety by avoiding chronic exposure to foreign materials and increases sustainability in medicine. For example, future implantable chips may be manufactured from resorbable polymers or bioresorbable electronics that degrade in a matter of months once therapy is complete. Biointegrated systems, where the delivery device duplicates or incorporates into body tissue, are also on the horizon. For example, drug-delivering biodegradable hydrogel patches can become integrated into the tissue matrix, or cell membrane-based nanocarriers can be designed to be biocompatible with the body. These are all part of broader healthcare efforts to place biocompatibility and sustainability at the forefront of medical device design(94,95).

### 5.4. Smart Packaging and Adherence Technology

Medication packaging is also becoming smarter, and the practice will probably transition out of clinical trials and into routine pharmacy dispensing. Smart packaging involves adding sensors or electronics to drug packages—bottles, blister packs, or injectors—to monitor medication compliance. Before long, many prescriptions will probably be dispensed with

electronic pill bottles that track each opening or blister packs that log when a pill is taken. These data can be forwarded to mobile apps to remind patients about their dosing schedules and transmit adherence reports to clinicians. Such packaging systems can significantly enhance the quality of clinical trial data and patient outcomes by facilitating correct dosing and timely administration. Smart packaging formats currently available work passively with minimal patient effort, such as automatically recording a timestamp whenever a drug is accessed. As the technology is developed further and costs decrease, we expect the integration of smart packaging into routine care. Future smart blister packs could even light up to remind patients of doses or lock to prevent double dosing, providing an additional safety net. This coupling of packaging and electronic surveillance will play a key role in improving drug compliance, particularly for treatments with precise dosing needs or significant abuse liability(96,97).

### 5.5. Wider Clinical and Therapeutic Applications

The future applications of smart drug delivery systems are expected to expand significantly in various therapeutic indications. While SDDS has already shown profound impact in diabetes (insulin automation), respiratory disease, and oncology, new applications are being investigated for other indications(98). For example, SDDS are being developed for neurology, including targeted delivery across the blood-brain barrier for Alzheimer's disease, illustrated by intranasal smart devices. In cardiology, smart patches that monitor cardiac markers and administer heart failure or hypertension drugs are being developed(99). SDDS can also play a key role in infectious disease treatment, i.e., long-acting implants for HIV or tuberculosis treatment, which would improve compliance in resource-poor settings(100). In the surgical arena, drug-eluting materials may promote wound healing or facilitate tissue regeneration, such as bioresponsive scaffolds that release growth factors when needed for tissue engineering. Another exciting area is theranostics—therapy and diagnostics combined—with nanoparticles that deliver drugs and have imaging agents to monitor drug distribution in real time. Wearable pumps that adjust drug delivery based on sensor feedback are another promising innovation, enabling real-time diagnostic and therapeutic functionality. The universality of SDDS is such that they may be applied to a wide range of conditions for which precise dosing is critical, yet again enhancing their potential(101).

## 6. GLOBAL MARKET GROWTH AND COMMERCIALIZATION

From a commercial perspective, the worldwide market for intelligent drug delivery is poised to witness robust growth in the next decade. Market analysts approximate that the SDDS market was valued at around $12 billion in 2024 and will continue to expand at a compound annual growth rate (CAGR) of 17% through 2034. The increasing prevalence of chronic conditions worldwide, the trend towards precision medicine, and consistent tech innovation in wearables and IoT fuel this expansion. North America is currently leading in SDDS adoption, with the United States adding around $5 billion to the market in 2024, which will rise four times by 2034. This can be attributed to strong healthcare infrastructure and active collaboration between the pharmaceutical and technology sectors. Europe and Asia are also investing heavily in smart drug delivery systems, having seen their potential in improving patient outcomes and healthcare efficiency. Collaborations between technology companies and pharmaceutical firms will be more common, as already witnessed by recent joint projects on smart inhalers and insulin products. Furthermore, big medtech and pharma corporations, such as Medtronic, Johnson & Johnson, and Novo Nordisk, are already working on smart injection and monitoring systems. Startups are also innovating, with new concepts like nano-robotic capsules and AI-powered drug platforms. With this momentum, SDDS are evolving from a niche innovation into a mainstream component of healthcare(102–104).

## CONCLUSION

Smart Drug Delivery Systems (SDDS) is a paradigm of precision medicine that harnesses the latest advances in nanotechnology, biomaterials, digital health, and artificial intelligence to redefine therapeutic delivery. SDDS accomplish spatiotemporal drug release with low systemic toxicity and off-target effects along with enhanced patient compliance due to individually tailored regimens. Advancements in the form of stimuli-sensitive nanocarriers, implantable microsystems, and artificial intelligence-driven closed-loop systems are the newest developments in the field that offer tailored solutions for as varied a disease as cancer to diabetes.

However, the road to widespread clinical adoption is not without hurdle. Cost- and reproducible manufacturing paradigms have to be developed in order to scale up nanocarriers and device-based systems. Combination products, particularly those involving software or AI, necessitate regulatory agencies to evolve in order to tackle the unique requirements of these products. Patient-centered design and long-term biocompatibility are no less necessary because the most sophisticated systems are of no value without usability and trust. Fair access and economic sustainability in the low-resource setting require novel business models and international cooperation.

To realize the true potential of SDDS in the future, five dimensions will require special research attention. First, hyper-personalized therapies will require integration with multi-omics and real-time biosensing to engineer adaptive dynamic systems that can respond to the physiology of individual patients. Second, next-generation biomaterials like

biodegradable, biointegrated, and biomimetic materials will be required to reduce long-term implant-related risks and environmental burdens. Third, expansion of AI-enabling autonomy by machine learning-enabled solutions ranging from nanoparticle production to dosing forecast algorithms will enable the creation of completely self-optimizing delivery platforms. Fourth, studies will have to expand clinical frontiers through SDDS innovation for recalcitrant therapeutic aims such as nervous system diseases (most importantly blood-brain barrier penetration), cardiovascular ailments, and global health priorities such as long-lasting anti-infectives. Finally, achieving translational synergy via interdisciplinary collaboration will be essential to justify regulatory pathways, demonstrate cost-effectiveness, and effectively implement SDDS into existing healthcare infrastructures.

As they come together, SDDS will arise from discontinuous niche medicines to mass therapy, reshaping healthcare paradigms. Through breaking down current barriers through collaborative research and cooperative development, the science has the ability to live up to its promise of safer, smarter, and lower-cost precision medicine, ultimately altering patient outcomes worldwide.

## CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

## AUTHOR CONTRIBUTIONS

Mohammad Seyedhamzeh contributed to the conceptualization and drafting of the manuscript. Sharareh Houshmandyar was responsible for manuscript editing. Mehrdad Hamidi supervised the project, revised the manuscript critically for important intellectual content, and is the corresponding author. All authors read and approved the final manuscript.

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