GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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From nanoparticles to robotic pills: The evolution of nanotechnology in drug delivery

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GSC Biological and Pharmaceutical Sciences, 2025, 32(01), 007-016

Publication history: Received on 25 May 2025; revised on 01 July 2025; accepted on 04 July 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.32.1.0261

Abstract

By allowing exact, targeted, and patient-centric treatments, nanotechnology has revolutionized drug delivery systems (DDSs). This paper tracks the evolution from passive nanoparticles (1980s) to active nanorobots and robotic pills, describing their development processes, applications, and dosage form examples. Along with a comparative analysis of targeting accuracy, bioavailability, patient compliance, and scalability, comprehensive methods for synthesizing, fabricating, and testing each dosage form are offered. Visual aids—including a timeline (1980s–2025) and a figure comparing dosage form mechanisms—show their evolution and function. Emphasizing clinical consequences, tables summarize marketed products, clinical trials, and pros/cons. These DDSs handle conventional therapy constraints—poor bioavailability, systemic toxicity, and low compliance—all the while contending with issues including biocompatibility, legal obstacles, ethical questions, and worldwide access inequalities. Future paths emphasize nanotechnology's capacity to transform medicine by including sustainable manufacturing, fair healthcare, and AI-driven systems.

Keywords: Nanotechnology; Drug Delivery; Nanoparticles; Nanorobots; Robotic Pills; Targeted Delivery; Precision Medicine; Biocompatibility

1. Introduction

Nanotechnology has changed drug delivery shifting from broad less effective methods to focused gentler systems [1]. This journey kicked off in the 1980s with liposome studies leading to the FDA's green light for Doxil in 1995, a liposomal nanoparticle to treat cancer [8]. This breakthrough sparked progress giving rise to nanorobots (2000s) and robotic pills (2010s), each boosting accuracy, effectiveness, and patient comfort [2]. These systems tackle issues in standard DDSs, like poor absorption unwanted effects, and low compliance, which hamper results in diseases such as cancer, diabetes, and brain disorders [9]. New inventions—DNA nanorobots to target tumors RaniPill for oral biologics, and PillBot for gut checks—show quick advances [10]. Worldwide, nanoparticle-based mRNA vaccines (e.g., Comirnaty) have changed how we respond to pandemics [11]. Rules (FDA EMA) adapt to cover nanomedicines [12]. Ethical worries, including fair access and privacy, are key [13]. This review breaks down the growth making, uses, and examples (on the market and in tests) of nanoparticles, nanorobots, and robotic pills backed by a timeline (1980s–2025) and a figure comparing how they work [14]. It looks into the pros, hurdles ethical impacts, and global reach predicting their role in tailored fair treatments [15]

Nanoparticles (1–100 nm) serve as carriers. These include liposomes polymeric nanoparticles (e.g. PLGA, PEG), dendrimers metallic nanoparticles (e.g., gold, silver), and hybrids (e.g., lipid-polymer) [16]. You can adjust their size and surface chemistry. They can cross barriers. This allows them to release drugs where needed [17]. Nanorobots are active systems. They can move, sense, and release drugs. External sources (e.g. magnetic fields, ultrasound) or internal sources (e.g., chemical, enzymatic) power them [18]. Robotic pills are tiny devices you can swallow. They deliver drugs . They

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have microneedles, microinjectors, or sensors. These target the GI tract to release drugs or diagnose issues [19]. These technologies mix materials science, bioengineering, robotics, and pharmacology. They aim to treat cancer, diabetes, brain disorders, and infections [20]. To develop them, scientists use computer models build prototypes, and test in clinics [21]. In medical use, they make drugs work better and cause fewer side effects [22]. Biohybrid nanorobots and AI-improved nanocarriers open up new possibilities [23].

2. Evolution of Nanotechnology-Based Drug Delivery Systems

2.1. Nanoparticles

2.1.1. Development

Nanoparticles first appeared in the 1980s with liposomes leading to Doxil's approval in 1995 to treat Kaposi's sarcoma [8]. The first systems relied on passive targeting through the enhanced permeability and retention (EPR) effect [24]. Progress brought about polymeric, metallic, dendrimer, and hybrid nanoparticles, which allowed for active targeting using ligands (such as antibodies and aptamers) [25]. New developments include nanoparticles that respond to stimuli (pH, temperature, enzymes), systems inspired by biology (like cell membrane-coated particles), and nanocarriers designed by AI for individualized treatment [26].

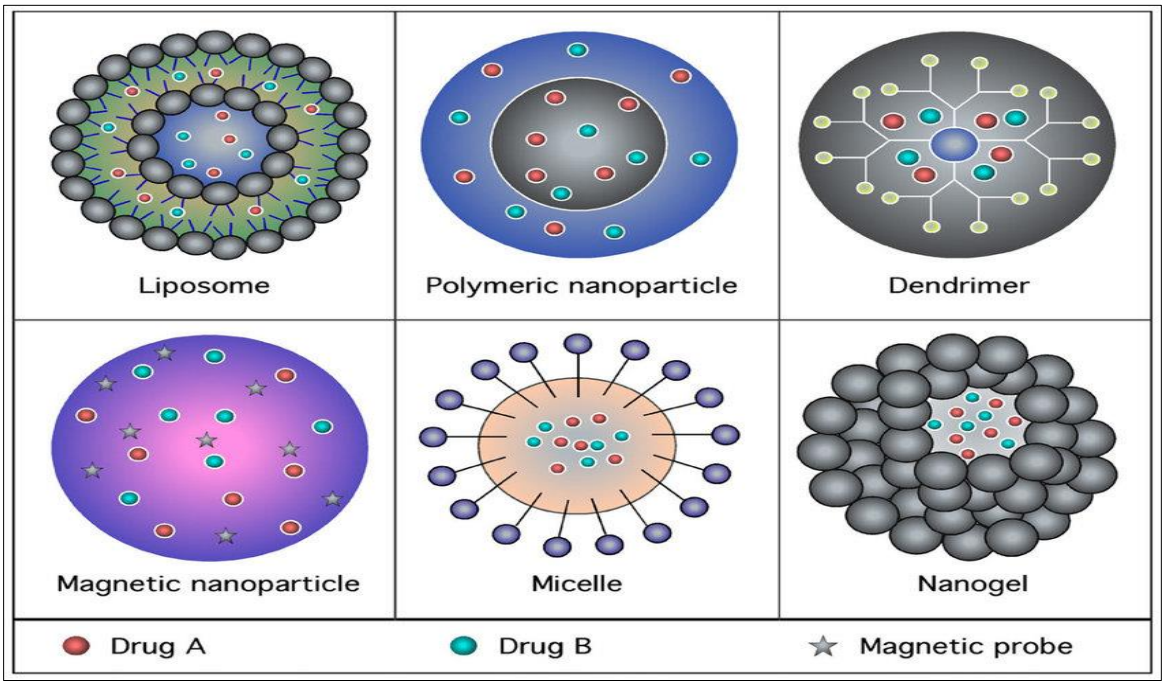

Figure 1 Schematic diagram representing the various types of nanoparticles use to develop MTIs. (5A) Liposome; (5B) Polymeric nanoparticle; (5C) Dendrimer; (5D) Magnetic nanoparticle; (5E) Micelle; (5F) Nanogel

2.1.2. Procedures for Development

Creating Materials

- Liposomes: Scientists form these by dissolving lipids in chloroform then evaporating to leave a thin film, which they hydrate with an aqueous buffer., they use reverse-phase evaporation by emulsifying lipids within a water-based phase [27].
- Polymeric Nanoparticles: Researchers create these through methods like single or double emulsion. They also use nanoprecipitation where polymers separate in a non-solvent, or solvent evaporation, which involves removing the solvent from a polymer-drug emulsion [28].
- Metallic Nanoparticles: Scientists create these using methods like chemical reduction such as reacting gold salts with sodium citrate. They also use green synthesis with plant extracts or rely on laser ablation techniques for making gold or silver nanoparticles [29].

- Dendrimers: These are made using either divergent synthesis, which starts from the core and moves outward, or convergent synthesis where the outer layers are built inward. Techniques like iterative reactions such as Michael addition, are applied [30].
- Top-Down Methods: Techniques like photolithography, electron beam lithography, and nanoimprint lithography allow precise size management within 10 to 100 nm [31].

Drug Encapsulation

- Added during production (like hydrophobic drugs within liposome layers) or after production through covalent coupling (using EDC/NHS methods) electrostatic attachment, or trapping [27].

Surface Changes Bound ligands (such as folate, anti-HER2, or RGD peptides) through methods like covalent attachment, click reactions, or electrostatic forces [32]. Adding PEG improves stealth features [33].

Characterization

- Researchers measured size, zeta potential, and polydispersity using dynamic light scattering methods as referenced in [27]. Experts examined morphology through tools like transmission electron microscopy or scanning electron microscopy, as noted in [29]. They studied drug release kinetics with HPLC or UV-Vis techniques as described in [34].

Preclinical Testing

- In Vivo: Researchers study biodistribution, pharmacokinetics (PK), and pharmacodynamics (PD) using mouse and rat models [36]. They check toxicity by looking at organ buildup, like in the liver or spleen [37].

- In Vitro: Scientists assessed cell uptake in cancer cell lines evaluated cytotoxicity using the MTT assay, and conducted experiments to study drug release, as mentioned in [35].

Scale-Up and Regulatory

- Good Manufacturing Practices (GMP) focus on keeping batches consistent [38]. To apply for IND approval, the FDA or EMA requires preclinical studies, production methods, and quality checks [39].

2.1.3. Applications

Chemotherapy (e.g., Abraxane) [40], imaging (e.g., iron oxide for MRI) [41], gene therapy (e.g., siRNA, CRISPR-Cas9) [42], vaccine delivery (e.g., mRNA vaccines) [43], and antimicrobial therapy (e.g., silver nanoparticles) [44] are all made possible by nanoparticles. They support combination therapies, protect payloads, and improve solubility [45]. Neurological treatments and tendon repair are emerging applications [46].

Examples of Dosage Forms

Marketed

- Doxil (liposomal doxorubicin 1995): Used to treat Kaposi's sarcoma and ovarian cancer [8].
- Abraxane (albumin-bound paclitaxel 2005): Treats breast and pancreatic cancers [40].
- Comirnaty (mRNA vaccine 2020): Developed to protect against COVID-19 [43].

In clinical testing

- mRNA-4157 (mRNA vaccine Moderna): In Phase II/III trials focusing on melanoma (NCT03897881) [47].
- AuroLase (gold nanoshells): Phase I trial underway to treat prostate cancer (NCT04240639) [47].

2.1.4. Limitations

Passive targeting lacks precision and demands higher doses, which can lead to toxicity [24]. Creating complex systems like dendrimers raises costs and adds challenges to replication [25]. Differences between patients such as variations in EPR, reduce how effective treatments can be [48]. Concerns over long-term safety involve buildup in the body and possible immune system reactions [49].

2.2. Nanorobots

2.2.1. Development

Nanorobots first appeared in the 2000s, spurred by Richard Feynman's 1959 concept [50]. Chemical propulsion, such as hydrogen peroxide breakdown, was employed in early designs [18]. Current systems (2010s–2025) use enzymatic triggers, light, ultrasound, or magnetic fields [23]. Conformational changes are used to target DNA nanorobots (Wyss Institute, 2018) [17]. Advanced nanorobots are magnetically guided and biohybrid (e.g., bacterially propelled) [35].

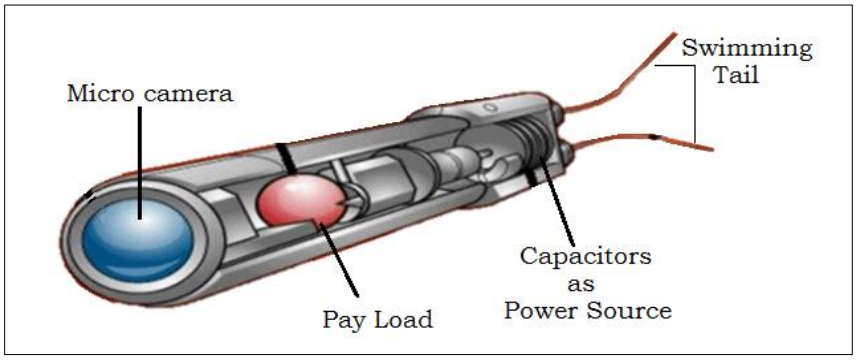

Figure 2 Components of Nano Robots

2.2.2. Procedures for Development

Material Selection

- Biocompatible materials, such as bacterial chassis, iron oxide, silica, gold, or DNA origami [18]. Biohybrid systems make use of motile bacteria or sperm, while magnetic nanorobots employ ferromagnetic cores [23].

Design of Propulsion

- **Chemical**: Catalytic surfaces (such as platinum for the breakdown of peroxide) [18].
- **Magnetic**: FeO_4 screws are rotated by external fields (such as Helmholtz coils, 1–10 mT, and 1–10 kHz) [35].
- **Ultrasound/Light**: Motion is driven by photothermal effects or acoustic waves (10–50 MHz) [36].
- **DNA-Based**: Base-pair interactions that are programmed to change conformation [17].

Drug Loading

- Drugs embedded in DNA scaffolds, conjugated to surfaces, or encapsulated in porous structures [23]. pH, enzymes, or temperature can cause release [17].

Fabrication

- **Bottom-Up:** Chemical synthesis for metallic nanoparticles or self-assembly for DNA nanorobots [18].
- **Top-Down:** For precise components, use photolithography, 3D printing, or nanostencil lithography [31].
- **Biohybrid:** Drug-loaded nanoparticles are used by synthetic biology to engineer bacteria [23].

Testing and Control

- ***In Vitro***: Vascular-like navigation in microfluidic channels [36]. MRI or fluorescence imaging [35].
- ***In Vivo***: Propulsion, targeting, and safety are evaluated using mouse tumor/stroke models [17]. Movement is guided by external controllers, such as magnetic fields [35].

Regulatory Preparation

IND applications are supported by preclinical data on biocompatibility, toxicity, and biodistribution [39]. Safety and dose-limiting toxicities are the main concerns of phase I trials [12].

2.2.3. Applications

Nanorobots enable deep-tissue delivery (e.g., tumor targeting, thrombolysis) [17], diagnostics (e.g., nanosensors) [37], and minimally invasive surgery (e.g., plaque removal) [18]. They cross barriers like the blood-brain barrier, offering potential for Alzheimer's and glioblastoma [23]. Emerging uses include dental care and environmental remediation [38].

Dosage Form Examples

- Not marketed (preclinical/early clinical) [17].
- **Current Clinical Trials**: o Phase I, ischemic stroke (NCT04487353) of the University of Hong Kong's Magnetic Nanorobots [47].
- **DNA Nanorobots**: Phase I, lymphoma (NCT04554849) (Wyss Institute) [47].

2.2.4. Limitation

Scalability, accurate control, and biocompatibility are still issues [23]. Toxic byproducts can result from chemical propulsion [18]. Magnetic coils and other external control systems are heavy [35]. Translation is limited by high fabrication costs and complicated regulations [17].

2.3. Robotic Pills

2.3.1. Development

Introduced in the 2010s, robotic pills combine oral delivery with microscale robotics [19]. Innovations include MIT's 2013 microneedle system, RaniPill's microinjector, and PillBot for GI diagnostics [20]. Recent advancements (2024–2025) feature magnetic actuation, wireless communication, and closed-loop systems [39].

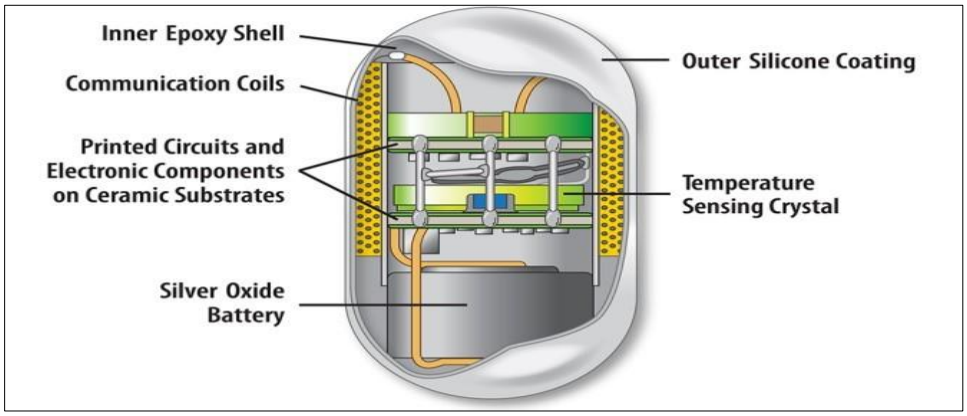

Figure 3 Diagram of Robotic Pills

2.3.2. Procedures for Development

Methods for Development

- **Material Design:** o Biodegradable polymers for capsule shells, such as chitosan, gelatin, and PLGA [19]. Biocompatible resins, silicon, or stainless steel are used in microneedles and injectors [20]. Gastric acid is prevented by pH-sensitive coatings, such as Eudragit [32].

Mechanism Integration

- **Microneedles:** Produced using 3D printing or MEMS etching (resolution: 10–100 μm) [20].
- **Microinjectors**: magnetic triggers (1–5 mT fields), springs, or chemical actuators (like CO2 release) [19].
- **Sensors:** pH/glucose sensors for diagnostic purposes or CMO cameras [20].

Drug Formulation

- Biomolecules (like insulin and adalimumab) are loaded into microneedles or reservoirs and stabilized with excipients (like trehalose) [32].

Assembly

- Microscale components are put together by robotic automation, 3D printing, or microfabrication [20]. Real-time control is made possible by wireless chips [39].

Testing

- In Vitro: GI models (pH gradients, synthetic mucus)
- In Vivo: Porcine models assess bioavailability, tissue penetration, and safety [19]. Diagnostic devices tested for imaging resolution [20].

Clinical Trials

- Phase I evaluates bioavailability and safety, Phase II assesses efficacy, and Phase III compares with standard treatments [12]. Scalability is guaranteed by GMP [39].

2.3.3. Application

Robotic pills can perform GI diagnostics (e.g., PillBot), deliver biologics (e.g., insulin, adalimumab) [19], and allow localized release for ulcers or colorectal cancer [21]. Cardiovascular treatments, microbiome modification, and oral vaccinations are examples of emerging applications [40].

Examples of Dosage Forms

- **Marketed**: None (clinical trial phase) [20].
- **Ongoing Clinical Trials**
- **RaniPill** (Rani Therapeutics): Phase I/II, octreotide (NCT04327999) [47].
  - **MIT Microneedle Pill** (MIT/Novo Nordisk): Phase I, insulin (NCT04566783) [47].
  - **PillBot** (Endiatx): Phase I, GI diagnostics (NCT04856813) [47].

2.3.4. Limitations

Adoption is hampered by high expenses, complicated regulations, and a small payload capacity [20]. Variable GI environments (e.g., pH, motility) challenge control [39]. Long-term concerns include device retrieval and patient acceptability [19].

Table 1 Summary of Dosage Form Examples

Dosage Form	Marketed Products	Ongoing Clinical Trials (Phase I–III)
Nanoparticles	- Doxil (1995): Kaposi's sarcoma [8] - Abraxane (2005): Breast, pancreatic cancer [40] - Comirnaty (2020): COVID-19 [43]	- mRNA-4157: Phase II/III, melanoma (NCT03897881) [47] - AuroLase: Phase I, prostate cancer (NCT04240639) [47]
Nanorobots	- None [17]	- Magnetic Nanorobots: Phase I, stroke (NCT04487353) [47] - DNA Nanorobots: Phase I, lymphoma (NCT04554849) [47]
Robotic Pills	- None [20]	- RaniPill: Phase I/II, octreotide (NCT04327999) [47] - MIT Microneedle Pill: Phase I, insulin (NCT04566783) [47] - PillBot: Phase I, GI diagnostics (NCT04856813) [47]

3. The Significance of Dosage Forms Based on Nanotechnology

- **Precision Medicine**: For autoimmune disorders and cancer, targeted delivery reduces toxicity [40].
- **Biological Barriers**: Robotic pills and nanorobots can pass through GI mucus and the blood-brain barrier [17].

- **Bioavailability**: By improving absorption, encapsulation lowers dosages [19].
- Patient Compliance: For chronic conditions, oral robotic pills increase adherence [20].
- **Multifunctionality:** Therapy and diagnostics are integrated by theranostic systems [18].
- **Sustainability**: Biodegradable materials lessen their negative effects on the environment [22].
- **Global Health**: Pandemics and low-resource environments are addressed by robotic pills and scalable nanoparticles [43].
- **Economic Impact:** Lower medical expenses result from fewer side effects [15].5. Comparative Analysis of Dosage Forms

Table 2 Advantages and Disadvantages

Dosage Form	Advantages	Disadvantages
Nanoparticles	- High clinical maturity (FDA-approved) [8] - Scalable manufacturing [27] - Versatile applications [40] - Cost-effective for simple formulations [25]	- Limited specificity (passive targeting) [24] - Systemic toxicity risks [48] - Reproducibility issues for complex systems [25]
Nanorobots	- Superior active targeting [17] - Deep-tissue penetration [35] - Low dosages reduce side effects [18] - Multifunctional [23]	- Preclinical stage [17] - Complex, costly fabrication [35] - Biocompatibility issues [23] - Bulky control systems [36]
Robotic Pills	- High patient compliance [20] - Enhanced bioavailability [19] - Active site-specific release [39] - Diagnostic capabilities [20]	- High manufacturing costs [20] - Limited payload capacity [39] - Regulatory complexity [19] - Variable GI performance [39]

Table 3 Comparative Features

Feature	Nanoparticles	Nanorobots	Robotic Pills
Size	1–100 nm	Nano- to microscale	Micro- to macroscale
Targeting	Passive/active	Active (propulsion)	Active (mechanical)
Bioavailability	Moderate	High	High
Patient Compliance	Moderate	Low	High
Payload Capacity	Moderate	Low to moderate	High
Clinical Maturity	High	Low	Moderate
Cost	Low to moderate	High	High
Manufacturing	Scalable	Complex	Complex

3.1. Visual aids

Table 4 Timeline of Drug Delivery System Milestones (1980s–2025)

Year	Milestone	Description
1980s	Liposome Research	Early liposome studies for drug encapsulation [8].
1995	Doxil Approval	First FDA-approved nanoparticle (liposomal doxorubicin) [8].
2000s	Nanorobot Concepts	Chemical propulsion nanorobots proposed [18].
2005	Abraxane Approval	Albumin-bound paclitaxel for cancer [40].
2010s	Robotic Pills Emerge	MIT's microneedle pill for insulin delivery [19].
2018	DNA Nanorobots	Wyss Institute develops DNA nanorobots for cancer [17].

2020	Comirnaty Approval	Lipid nanoparticle mRNA vaccine for COVID-19 [43].
2023	RaniPill Trials	Phase I/II trials for oral biologics [47].
2024	Biohybrid Nanorobots	Bacteria-propelled systems for deep-tissue delivery [35].
2025	Closed-Loop Pills	AI-driven robotic pills with real-time monitoring [39].

Table 5 Comparison of Dosage Form Mechanisms

Dosage Form	Mechanism	Illustration
Nanoparticles	Passive (EPR) or active (ligand-mediated) targeting; drug release via diffusion or stimuli (e.g., pH) [24].	Encapsulated drug in liposome/polymer shell, targeting tumor via EPR or ligands.
Nanorobots	Active propulsion (magnetic, ultrasound, chemical); targeted release via environmental cues [17].	Magnetic nanorobot with drug payload, navigating vasculature to tumor.
Robotic Pills	Mechanical delivery (microneedles, injectors); site-specific release in GI tract [20].	Capsule with microneedles injecting biologics into GI mucosa.

Challenges and Limitations

- **Biocompatibility**: To prevent immunological reactions, nanoparticles and nanorobots need biodegradable materials [23].
- **Regulatory Obstacles**: The FDA and EMA closely monitor active systems [12].
- **Scalability and Cost**: Commercial viability is limited by complex fabrication (e.g., DNA nanorobots, MEMS) [20].
- **Control and Stability**: It can be difficult to navigate in dynamic environments (such as the GI tract or blood flow) [36].
- **Reproducibility**: Batch variability is a problem for complex systems [25].
- **Patient Variability**: Efficacy is impacted by physiological variations [48].
- **Ethical Concerns:** Issues with autonomy, privacy, and fair access come up [13].
- **Environmental Impact**: Materials that are not biodegradable present hazards [22].
- **Long-Term Safety**: Longitudinal studies are necessary for chronic exposure [49].

Future directions

- **AI Integration**: Dosing optimization and real-time navigation [23].
- **Closed-Loop Systems**: Self-governing drug release and biomarker monitoring [39].
- **Hybrid Systems**: combining the accuracy of nanorobots with the scalability of nanoparticles [17].
- **Sustainable Manufacturing**: Recyclable materials and green synthesis [22].
- **Clinical Translation**: Partnerships and regulations are streamlined [12].
- **Ethical Access**: Cost-cutting measures for worldwide fairness [13].
- Genomic integration for customized treatments is a component of [15].

4. Conclusion

Precision and patient-centered needs are driving a revolutionary era in drug delivery with the development of nanoparticles, nanorobots, and robotic pills. Clinical maturity is provided by nanoparticles, active targeting is provided by nanorobots, and bioavailability and compliance are improved by robotic pills. Tables, visual aids, and thorough development processes demonstrate their creativity and clinical advancement. These DDSs hold great promise for improving diabetes, cancer, and global health, despite obstacles like biocompatibility, cost, and ethics. Their future will be shaped by AI, ethical frameworks, and sustainable manufacturing, guaranteeing individualized, equitable healthcare.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest related to this review article.

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