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REVIEW **Open Access**

Multifaceted applications of micro/nanorobots in pharmaceutical drug delivery systems: a comprehensive review

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Abstract

Background Drug delivery systems (DDSs) encompass a wide range of methods, including oral, injectable, and topical routes of administration, all tailored to meet specific patient needs. Micro and nanorobots, equipped with pioneering propulsion mechanisms that convert external energy sources into precise movements, have revolutionized drug delivery. This cutting-edge technology ensures highly efficient drug delivery, particularly when targeting specific targets within intricate physiological environments. In contrast to traditional drug delivery approaches that rely on bloodstream circulation, engineered micro/nanorobots have autonomous mobility, enabling drug delivery to previously unreachable areas.

Main body of the abstract Integrating micro/nanorobots into drug delivery raises vital safety and biocompatibility issues. These encompass material selection, degradation in-vivo, overcoming biological barriers, controlled movement, external interference, immune response, chemical reactions, systemic effects, long-term impact, and real-time monitoring. While micro/nanorobots hold immense transformative potential, they confront significant hurdles in their journey toward practical applications. Chief among these challenges are concerns regarding biocompatibility, ensuring that these tiny devices do not trigger adverse reactions. Long-term safety remains a critical issue, as understanding the effects of prolonged exposure and potential accumulations within the body and navigating complex biological environments with precision is another obstacle.

Short conclusion The paper summarizes how to explore the various ways in which micro/nanorobots can be employed to enhance drug delivery, including their precision, targeting capabilities, and adaptability to different physiological conditions. Additionally, the review seeks to highlight the transformative potential of these technologies and their impact on the pharmaceutical industry.

Keywords Micro/nanorobots, Targeted drug delivery, Novel drug delivery systems, Real-time monitoring

Background

Drug delivery systems (DDSs) encompass diverse approaches for administering therapeutic agents. These methods involve various routes of drug administration, encompassing oral, injectable, and topical routes, tailored to specific patient needs [1]. DDSs incorporate a range of drug formulations and delivery devices, addressing the complexities of biotechnology-based therapeutics like proteins and peptides. Advanced techniques, such as cell and gene therapies, offer precision in treatment delivery. Nanoparticles play a pivotal role, serving as carriers

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for drugs and even as pharmaceuticals and diagnostics themselves [2]. Targeted drug delivery, particularly in cancer therapy, has seen significant progress. Overcoming blood–brain barrier challenges is vital, and DDS refinements pave the way for personalized medicine. The ideal DDS aims to optimize therapeutic efficacy while minimizing side effects [3].

Micro and nanorobots have emerged as revolutionary drug delivery systems, leveraging innovative propulsion mechanisms that convert external energy sources into precise movements. This advanced technology offers exceptional efficiency in drug delivery, especially when targeting specific sites within complex physiological environments [4]. These micro and nanobots have demonstrated remarkable capabilities, including the encapsulation, transport, and direct delivery of therapeutic substances to disease sites. This targeted approach not only enhances therapeutic efficacy but also significantly reduces systemic side effects associated with potent drugs. In essence, micro and nanobots represent a transformative leap in drug delivery, enabling precise, site-specific treatment with minimal collateral impact [5]. Unlike conventional drug delivery methods relying on bloodstream circulation for drug transport, engineered micro/nanorobots possess autonomous mobility, facilitating drug delivery to otherwise inaccessible regions [6]. These micro/nanorobots are powered either externally, through magnetic fields, light, acoustics, or electric fields, or internally, via chemical reactions. While micro/nanorobots hold promising potential, the majority of current research remains confined to in-vitro experiments, with in-vivo investigations still in their nascent stages. Further biological studies are imperative to substantiate the in-vivo drug delivery efficacy of micro/nanorobots [7].

However, PLA (Polylactic Acid) and TPU (Thermoplastic Polyurethane) are two different types of biocompatible polymers that play important roles in the development of nanorobots/microrobots for drug delivery systems [8]. PLA is a biodegradable and biocompatible polymer derived from renewable resources, such as corn starch or sugarcane which can be used to construct the structural components of nanorobots/microrobots, providing a stable and non-toxic framework for drug delivery systems. Therefore, PLA-based nanorobots can be designed to release drugs at a controlled rate as the polymer gradually degrades, making it suitable for sustained drug delivery [9]. Its versatility and compatibility with various drug formulations make it a popular choice for encapsulating and delivering therapeutic agents. On the other hand, TPU is another biocompatible polymer known for its flexibility and durability which can be used to create flexible components or coatings for nanorobots/microbots, allowing for improved mobility and adaptability within the body's complex environment [10]. TPU-coated nanorobots can navigate tight spaces, overcome obstacles, and potentially target specific tissues or cells more effectively. Its ability to withstand mechanical stress and maintain stability under different physiological conditions makes TPU valuable in enhancing the functionality and maneuverability of drug-delivery microrobots [11]. In drug delivery systems, both PLA and TPU can be utilized to design and manufacture nanobots/microbots tailored for specific applications.

The review aims to provide a thorough examination of the diverse roles that micro/nanorobots play in drug delivery, encompassing their design, functionalities, and mechanisms of action. Furthermore, it seeks to elucidate how these innovative systems enable targeted drug delivery, controlled release, and navigation within physiological environments. Additionally, the review assesses the challenges and advancements in this field, including biocompatibility, safety concerns, and recent technological developments. Ultimately, it aspires to offer insights into the transformative potential of micro/nanorobots in revolutionizing drug delivery and advancing healthcare.

Main text

Types of micro/nanorobots in pharmaceutical drug delivery systems

The types of micro/nanorobots that are prevalent in current pharmaceutical drug delivery technologies can be classified into two broad types as shown in Tables 1 and 2.

Magnetic small-scale robots hold significant promise in the biomedical field due to their advantages in actuation. Recent research has witnessed notable advancements in the design, fabrication, and application of these devices, aiming to enhance their performance for potential clinical use [12]. An overview of recent progress in small-scale biomedical robots has been reviewed and studied emphasizing their development, capabilities, and existing challenges. It also suggests alternative biomedical applications for some technologies. The study of Koleoso et al., 2020 underscores the need for continued efforts to enhance the functionality and reliability of these robots, particularly in clinical contexts, and offers recommendations for advancing their commercialization [13]. According to Azar et al., 2020, the essential components of nanorobots, including sensors, actuators, and nano controllers, draw upon previous research to showcase diverse designs. It advances beyond theoretical discussions to delve into the practical aspects of manufacturing and implementation. Significantly, it emphasizes recent innovations in drug delivery, detection, and manipulation, providing insights into their motion mechanisms and the current manufacturing methods in use [14].

Table 1 Types of micro/nanorobots based on size

Types	Classification based on size
1. Microbots	– Typically, 1 μm to several hundred μm in size – Larger than nanoparticles but smaller than macroscopic robots – Suited for navigating through blood vessels and tissues
2. Nanorobots	– Typically, in the nanometer (nm) to micrometer range – Substantially smaller than microbots – Ideal for precise targeting at the cellular or molecular level

Table 2 Types of micro/nanorobots based on functionality

Types	Functionalities
1. Active Propulsion Robots	– These micro/nanorobots possess self-propulsion mechanisms to navigate within the body – Examples: Microswimmers, Microrobotic capsules, Light-powered microbots, Magnetic field-driven microbots, Acoustically-driven microbots, and Chemically-powered microbots
2. Passive Transport Robots	– These micro/nanorobots rely on external factors or carriers for transport within the body – Examples: DNA nanorobots, Nanoparticle-based carriers, Molecular shuttles, and Biomolecule carriers

Control and navigation strategies for nanorobots are explored in-depth, emphasizing the importance of mathematical positioning concepts in modeling these intricate devices [15]. Several studies presented various algorithms that enable precise control, underscoring their significance in the field. Furthermore, studies presented numerous applications that underscore the effectiveness of nanorobots across various domains. These applications encompass a wide range of functions, including diagnostics, treatments, target detection, and even complex surgical missions. These devices serve as a crucial link between theoretical analyses and practical manufacturing approaches [7, 14]. Importantly, it sheds light on future implementation concerns and emerging research gaps, emphasizing the need for continued investigation and innovation [14]. In a nutshell, the practical integration of nanorobots can be implemented in critical areas such as optical surgeries, cell manipulation, and cancer treatment. It contributes significantly to the advancement of nanorobotics and its potential impact on healthcare and other fields.

Targeted drug delivery mechanisms using micro/nanorobots

The use of micro/nanorobots capable of efficiently harnessing a variety of energy sources to facilitate motion has the potential to bring about a significant transformation in the pharmaceutical field, particularly in the realm of targeted drug delivery. Through the precise delivery to specific tissues or anatomical sites and controlled release mechanisms, drugs can be directed toward their intended destinations [16]. Targeted delivery encompasses a range of actuation energy sources, including self-propulsion via substances like hydrogen peroxide and enzymes, external propulsion driven by factors such as light, electricity, acoustics, and magnetic fields, as well as propulsion driven by motile microorganisms like bacteria, sperm cells, contractile cells, and immune cells as shown in Fig. 1.

Targeted and/or precise drug delivery is generally processed by using two major technologies—exogenous power-driven method and endogenous power-driven methods.

Exogenous power-driven technology

In exogenous power-driven Micro/Nanorobots, due to their micro/nano-size, drug-delivery robot systems face the challenge of countering Brownian motion to achieve autonomous movement within complex bodily fluids. According to Hu et al., 2020, an external power source is typically employed to enable the controlled and coordinated locomotion of these micro/nanorobots. Commonly utilized sources of external power include magnetic fields, electric fields, light energy, acoustic waves, and heat energy [17–21]. A combination of these driving modes in practical design is often employed to create micro/nanorobots with diverse functionalities [7]. Magnetic propulsion is one of the exogenous power-driven methods to prepare Micro/Nanorobots in drug delivery which often involves the design of helical swimmers, which are inspired by the flagella of micro-organisms [17]. These helically shaped micro/nanorobots mimic the

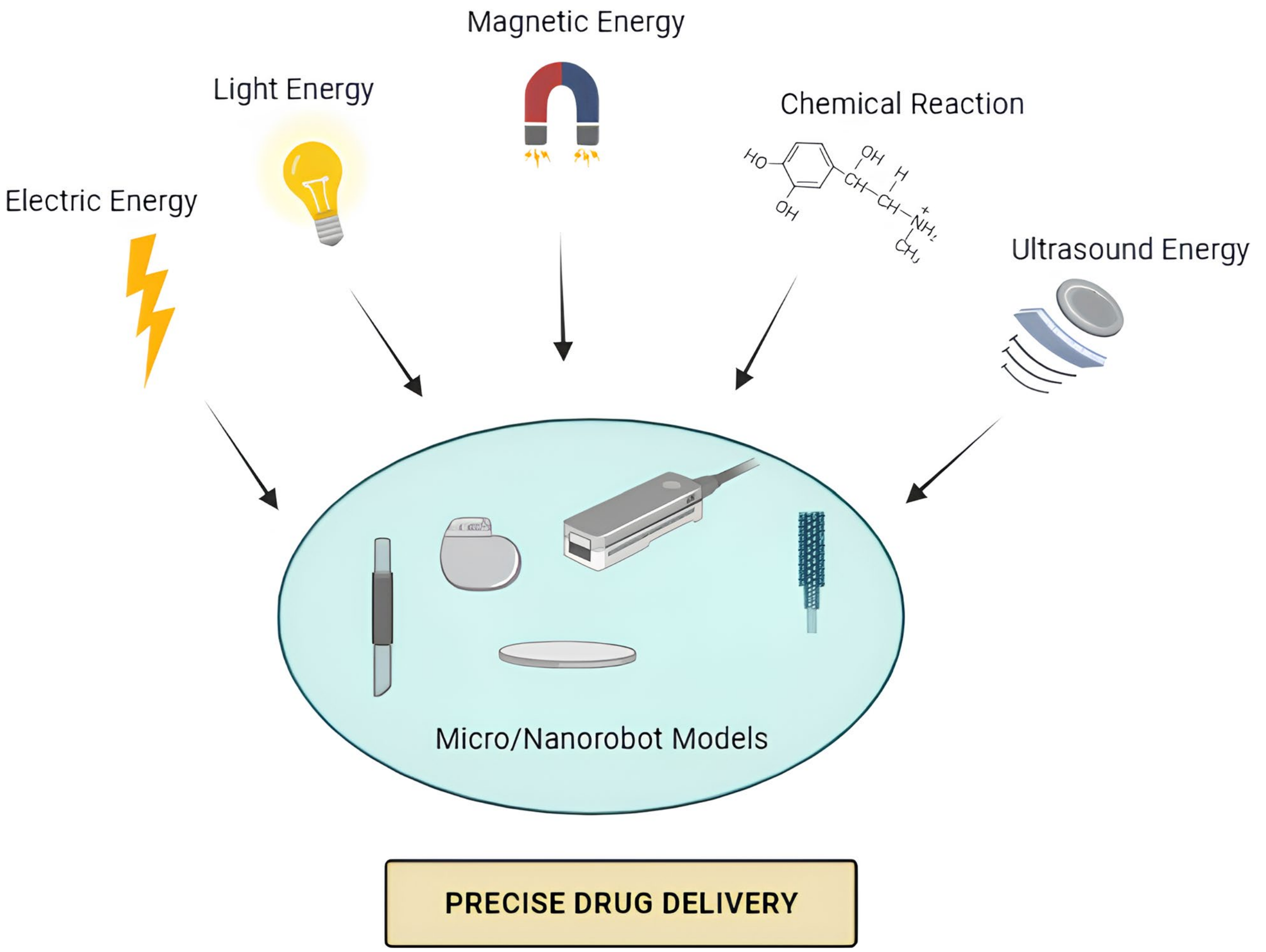

Fig. 1 Energy sources to design and develop micro/nanorobots for precise drug delivery

rotary corkscrew motion of bacterial flagella, enabling them to move through bodily fluids through interaction with external magnetic fields [22]. Researchers frequently combine these artificial bacterial flagella (ABF) with drug-loaded liposomes for drug delivery applications. For example, in a study conducted by Qiu et al. in 2014, they developed a microrobot consisting of two components. The first component is a titanium-coated ABF that enables precise 3D navigation within fluids when subjected to rotating magnetic fields. The second component is an outer temperature-sensitive liposome that controls the release of the drug based on temperature regulation. This innovative approach shows potential for enhancing targeted drug delivery in pharmaceutical applications [7, 23]. Electric field propulsion is also a widely used method in micro/nanorobotics, offering precise control and versatile applications in drug delivery and other fields [7]. Another significant illustration of exogenous power-driven micro/nanorobots is found in the Janus colloidal system. This system utilized a combination of electric and magnetic energy to facilitate independent movement and cargo retrieval [24]. It consists of metal-dielectric Janus colloids that respond to a high-frequency electric field (0.5–2.5 MHz). These colloids are characterized by a hemisphere coated with nickel, allowing them the ability to be guided in a specific direction by a magnetic field. This capability facilitates precise cargo delivery by predefining the path that the micro/nanorobot will follow. Rahman et al., 2017 introduced a rotational nanomotor structure using carbon nanotubes, which exhibited rapid responsiveness and ultra-high-speed movement when exposed to an electric field [25]. This motion was driven by the alignment of water dipoles induced by the electric field, demonstrating exceptional performance in water. However, its behavior in simulating more complex human systems or body fluids remained unexplored. Incorporating multiple energy sources, nanoparticles can achieve directional movement. Guo et al., 2018 also presented an approach for regulating the movement of catalytic nanomotors through the application of electric fields in conjunction with light energy [18]. In brief, electric field propulsion in micro/nanorobotics offers exciting possibilities for precise and programmable movement. The Janus colloidal system, with its dual responsiveness to electric and magnetic fields, exemplifies the potential for autonomous cargo delivery [26]. Carbon nanotube-based nanomotors exhibit rapid movement under electric fields, although their performance in complex biological environments requires further investigation. Finally, the combination of electric fields and light energy provides a controllable means to steer catalytic nanomotors [7, 26]. These advancements hold great promise for applications in drug delivery and other fields where precise, directed movement at the micro/nanoscale is essential. Light energy serves as another frequently employed method in micro/nanorobotics, offering high controllability and programmability, typically used in a supplementary role. Wang et al., 2018 studied that it enables directional movement of nanorobots through the modulation of light parameters such as frequency, polarization, intensity, and propagation direction [19]. A notable example is the work of Zhan et al., 2019 who harnessed the linear dichroism property of Sb_2Se_3 nanowires to create an artificial swimmer. This swimmer incorporated two cross-aligned dichroic nanomotors, and its movement was guided by adjusting the polarization direction of incident light [27]. This approach showcases the potential for precise control of nanorobot movement using light energy, making it a valuable tool in micro/nanorobotic applications. Light energy not only serves as a direct driving force for micro/nanorobots but can also catalyze redox reactions within them, leading to propulsion through the generation of chemical gradients or bubbles [28, 29]. For instance, Wang et al., 2019 developed a Cu_2O@N-doped carbon nanotube (Cu_2O@N-CNT) micromotor powered by glucose and activated by visible-light photocatalysis [30]. This micromotor exhibited several advantages, including non-toxicity, high biocompatibility, and environmental friendliness. It showcased impressive movement and 3D motion control within a biological environment. However, challenges persist when transitioning to in-vivo applications, mainly due to the limited ability of visible light to penetrate tissues [7, 30]. Utilizing an external power source, ultrasound power-driven micro/nanorobots show great potential in the field of advanced targeted drug delivery. Their outstanding biocompatibility and dependability make them a promising option, and they rely on external power-driven technology for their functionality. Commonly, nanowires, typically composed of gold, serve as the primary carriers for these ultrasonically driven nanorobots [20]. The template electrodeposition method plays a pivotal role in the design of ultrasound-propelled micro/nanomotors. This method involves creating a concave cavity at one end of the nanomotor through the deposition of a sacrificial copper layer. When subjected to ultrasound waves directed at the concave end, the nanomotor is propelled forward by the resulting pressure gradient [31]. Furthermore, ultrasound is frequently integrated with magnetic fields to enable precise control. For example, Victor and his team devised a magnetically guided three-segment nanowire motor with Au–Ni–Au segments, harnessing ultrasound for propulsion [32]. Changing the magnetic field's orientation enables ultrasound-propelled particles to move in all directions. The feasibility of precise drug delivery has been confirmed by introducing a polymeric section containing pH-sensitive drugs into the nanomotor. In acidic conditions, these drugs can be released, improving the selectivity of drug delivery. Additionally, Garcia-Gradilla et al., 2014 have developed an ultrasound-propelled nanorobot featuring four segments, including Au-Ni-Au and Au wire components [33]. This innovative approach also showcases the versatility and potential of ultrasound-powered nanorobots for advanced drug delivery applications.

Endogenous power-driven technology

In endogenous power-driven approaches, nanorobots rely on endogenous power sources for self-propulsion, primarily driven by chemical or biological reactions [34]. These micro/nanorobots are typically asymmetric and often coated with catalysts to harness continuous chemical energy from their surroundings. A prevalent approach involves converting chemical energy into a driving force using redox reactions, with the decomposition of hydrogen peroxide being a widely employed method. Hydrogen peroxide possesses an unstable chemical bond that readily breaks down into water and oxygen when catalyzed by various agents like metals, enzymes, or an alkaline environment. This concept has been extensively employed in nanorobot designs, including bimetallic nanorods, hollow Janus particles, vesicular polymers, and more [35–37]. These nanorobots hold great promise, particularly in the field of targeted drug delivery [38, 39]. Janus particles, a class of particles with distinct compositions and structures on their two hemispheres, have also contributed to this field. Wu and colleagues, for instance, engineered polymer multilayer Janus capsules capable of self-propulsion using 0.1% hydrogen peroxide as fuel at physiological temperatures [36]. This approach underscores the potential of nanorobots powered by chemical reactions, opening exciting avenues for various applications, including targeted drug delivery. While the concept of using chemical energy conversion has been extensively explored, its practical application within living organisms has been constrained due to the inherent toxicity of the commonly employed "fuel," hydrogen peroxide [40]. Researchers have sought alternative, safer materials to power nanorobots. One such substitute is magnesium, renowned for its high biocompatibility. Magnesium can react with water to produce bubbles, serving as a propellant, making it a promising replacement for the hazardous hydrogen peroxide [40, 41]. Another approach involves harnessing biocompatible enzyme-catalyzed reactions for self-propulsion. This method utilizes non-toxic fuels like glucose and urea to drive nanorobots. For instance, researchers developed a core–shell nanorobot based on mesoporous silica, demonstrating self-propulsion capabilities in ionic media [43]. They functionalized the nanorobot with urease, an enzyme that catalyzes the breakdown of urea into carbon dioxide and ammonia. This enzymatic reaction allowed the nanorobot to move autonomously and release drugs. Importantly, when loaded with Doxorubicin (Dox), these nanorobots exhibited remarkable efficacy against HeLa cells. This success can be attributed to the synergistic effects of enhanced drug release and the presence of ammonia generated through the catalytic reaction [42, 43]. These inventive strategies showcase the potential of utilizing biocompatible materials and enzyme-catalyzed reactions to power nanorobots, thereby mitigating safety concerns and advancing their application in drug delivery within biological systems. Endogenous chemical energy propulsion offers an advantage by minimizing the need for constant micro/nanorobot control, focusing instead on guidance toward the target, often via magnetic attraction. This approach uses gas generated from chemical reactions to reverse robot movement, well-suited for the gastrointestinal tract. However, chemical energy-driven nanorobots have drawbacks. Controlling their direction proves challenging, and they are sensitive to ionic environments, potentially disrupting motion. A significant limitation is their power continuity; they may exhaust energy as reactions proceed. Moreover, safety concerns surround the "fuel" and reaction products when applied within organisms, posing a substantial obstacle to their practical use [7]. These issues warrant further investigation and research in the future to address these challenges and unlock the full potential of chemical energy-driven self-propelled nanorobots in various applications, including targeted drug delivery within living organisms.

The comparison between exogenous and endogenous power-driven Micro/Nanorobots in Pharmaceutical drug delivery systems has been detailed in brief in below Table 3.

Apart from these types of micro/nanorobots, 4D printed micro/nanorobots are also some of the promising approaches in pharmaceutical DDS. 4D printed nano/microrobots are innovative vehicles for drug delivery in the pharmaceutical field [7, 44]. These tiny robots are constructed using advanced 4D printing technology, which allows them to change shape or behavior in response to external stimuli.

Safety and biocompatibility considerations for micro/nanorobots in drug delivery systems

Incorporating micro/nanorobots into DDS brings forth critical safety and biocompatibility concerns that must be addressed for successful application within the human body. These concerns encompass various aspects of nanorobot design, function, and interaction with biological systems. Key considerations include—biocompatible materials, in-vivo degradation, biological barriers, controlled mobility, external interference, immune response, chemical reactions, systemic effects, effects on long-term use, and real-time monitoring and feedback mechanisms.

The biocompatible materials used in nanorobot construction or designs must be ensured that the materials are non-toxic and biocompatible is paramount. Materials should not trigger adverse immune responses or

Table 3 Simplified comparison between exogenous and endogenous power-driven micro/nanorobots in pharmaceutical DDS

Aspects	Exogenous power-driven Micro/Nanorobots	Endogenous power-driven Micro/Nanorobots
Power source	External energy sources (e.g., magnetic fields, ultrasound)	Internal energy sources (e.g., chemical reactions, enzymes)
Control	Requires external control and guidance mechanisms (e.g., magnetic field manipulation)	Self-propelled and guided by internal processes or cues
Navigation	Controlled externally, often using precise guidance systems	May exhibit less precise navigation, influenced by internal conditions
Energy supply	Constant energy supply required from external sources	Utilizes internal energy generation, potentially limited by available substrates
Targeted drug delivery	Achievable with precise external control	Potential for targeted delivery, guided by internal conditions
Safety concerns	Limited safety concerns related to the energy source	Safety concerns related to the choice of reactants and products
Potential for in vivo use	Commonly used in controlled laboratory settings	Holds promise for in vivo applications, subject to further research
Examples	Magnetic or ultrasound-guided nanorobots	Enzyme-catalyzed nanorobots using the body's chemicals

tissue damage [45]. Considering in-vivo degradation, the nanorobots should be designed to degrade naturally or be eliminated from the body without leaving harmful residues or by-products inside the physiological systems [5]. Taking biological barriers into account, several research suggested that overcoming barriers such as the blood–brain barrier (BBB), and ensuring that micro/nanorobots can safely traverse them without causing damage is crucial for targeted drug delivery [46, 47]. According to Arvidsson and Hansen, 2020, it must be noted that nanorobots must be controlled to prevent unintended movement and potential harm to healthy tissues. Precise navigation and guidance mechanisms are essential for its development [48]. Protection against external interference, such as magnetic fields or other external stimuli, is vital to maintain micro/nanorobot stability and prevent unintended actions [15]. Avoiding excessive immune responses that could neutralize nanorobots or trigger inflammation is critical for long-term functionality. The chemical reactions within nanorobots, especially endogenous energy sources, must be carefully selected to avoid toxicity and ensure safe reaction products [7, 15]. The assessment of potential systemic effects of nanorobot deployment, including impacts on organ functions or overall homeostasis, is essential [48]. Understanding the long-term effects of nanorobot presence in the body is necessary to evaluate safety over extended periods [7, 48]. Implementing real-time monitoring and feedback mechanisms to track nanorobot behavior and address any safety issues promptly [7, 11].

Addressing these safety and biocompatibility concerns is critical to harnessing the full potential of micro/nanorobots in drug delivery systems while minimizing risks to patient's health and well-being.

Overcoming the limitations of endogenous and exogenous power-driven micro/nanorobots

However, endogenous/exogenous systems may have limitations in terms of biocompatibility. 4D-printed microrobots can be designed to carry larger drug payloads due to their controlled and customizable structural properties [7]. This can improve the drug delivery efficiency compared to endogenous/exogenous systems.

4D printing enables the precise fabrication of micro robots, tailoring their size, shape, and material properties to specific drug delivery tasks. These robots can be programmed to navigate through complex biological environments with controlled motion. They can swim, crawl, or even fold and unfold to reach target locations [44]. 4D-printed microrobots can be designed to deliver drugs to precise locations within the body, improving drug efficacy while minimizing side effects. They can respond to various stimuli, such as changes in temperature, pH, or magnetic fields, allowing for on-demand drug release. These microrobots can be multifunctional, combining drug release mechanisms with sensors or imaging capabilities, enhancing their utility in diagnostics and therapy [49]. Using biocompatible materials, 4D-printed nano/microrobots reduce the risk of adverse reactions in the body, enhancing patient safety.

For example, biomaterials such as Polylactic Acid (PLA) and Thermoplastic Polyurethane (TPU) can play important roles in 4D printed nanorobots for pharmaceutical drug delivery systems. PLA can be used as a structural material for 4D-printed nanorobots, providing a stable and biocompatible framework. Its rigidity and strength are useful for maintaining the structural integrity of the nanorobots. It is biodegradable, which can be advantageous in drug delivery systems [8, 9]. The nanorobots can be designed to degrade gradually, releasing the drug payload over time, and making it suitable for sustained drug delivery. Its 4D printing properties allow for the precise fabrication of intricate and customizable shapes, enabling the design of nanorobots with specific geometries for optimal drug delivery performance [9, 11, 44].

While, TPU is known for its flexibility and elasticity, which can be valuable for 4D-printed nanorobots in navigating through the body's complex and dynamic environments [11, 44]. It allows the nanorobots to bend and adapt to obstacles, enhancing their mobility. It can be used as a coating or an outer layer for the nanorobots. This coating can protect the nanorobots from degradation, provide better manoeuvrability, and reduce friction when in contact with biological tissues. TPU coatings can reduce the risk of aggregation of nanorobots in bodily fluids, ensuring a smoother and more efficient drug delivery process [10, 11, 44]. It can be incorporated into the 4D printing process to create components with shape-changing capabilities in response to external stimuli, improving the nanorobots' ability to reach target locations and release drugs as needed. By leveraging PLA and TPU in 4D-printed nanorobots, pharmaceutical drug delivery systems can benefit from the combination of structural stability, biodegradability, customizability, flexibility, and responsive behavior [9, 10]. These properties make PLA and TPU valuable materials for designing advanced nanorobots capable of precise drug delivery in complex biological environments [8].

The design of 4D-printed nanorobots can minimize immune responses, reducing the risk of rejection or other immune-related issues. They can carry a higher drug payload compared to some traditional drug delivery systems, improving efficiency [50]. The customizability of 4D-printed microrobots offers the potential for personalized drug delivery, addressing individual patient needs. These robots can be engineered to reduce the risk of aggregation in bodily fluids, ensuring smooth drug transport.

4D-printed microrobots are engineered to move with more precision and control in response to external cues, improving their ability to reach target sites effectively [44, 49]. Endogenous systems may not offer the same level of control. 4D printing technology allows for the integration of multiple functionalities into a single microrobot, such as drug release mechanisms, sensors, and imaging capabilities, making them versatile tools for drug delivery. Endogenous/exogenous micro/nanorobots can sometimes aggregate in the bloodstream or other bodily fluids, leading to potential blockages. 4D-printed microrobots can be designed to minimize aggregation risks. 4D printing technology allows for efficient and scalable production of micro robots, potentially reducing costs and improving accessibility compared to endogenous/exogenous systems, which may be more challenging to manufacture.

Recent insights on in-vivo *applications of micro/nanorobots drug delivery*

Several kinds of research are still being undertaken on animal models to demonstrate the use of micro/nanorobots in targeted drug delivery systems, however, the studies on human volunteers are yet to be done to draw clear justification for the use of these technologies in clinical phase trials. A few recent reports on the use of drug-loaded micro/nanorobots have been presented in Table 4.

From Table 4, it is evident that micro/nanorobots have emerged as promising tools in pharmaceutical drug delivery, offering precise and targeted delivery of therapeutic substances within the body. These tiny robotic systems, typically at the nanoscale, provide several key advantages in drug delivery, such as, (a) they can navigate through complex biological environments and deliver drugs directly to the target site, minimizing off-target effects and reducing the required drug dosage [4, 7], (b) they offer unparalleled precision in drug release, enabling controlled and on-demand drug delivery, which is especially valuable for diseases with fluctuating symptoms [7, 16], (c) they can carry poorly water-soluble drugs, enhancing their solubility and bioavailability, thereby improving therapeutic outcomes [56], (d) by reducing systemic exposure to drugs, micro/nanorobots can minimize side effects and toxicity, improving patient tolerance to treatment [7], (e) some of them are equipped with sensors that enable real-time monitoring of physiological parameters, allowing for adaptive drug release in response to changing conditions [7, 16], (f) they facilitate the delivery of multiple drugs simultaneously or sequentially, enabling combination therapies to target multiple aspects of a disease [7], (g) they can traverse biological barriers, such as the blood–brain barrier, enabling the delivery of drugs to previously inaccessible regions [12], and lastly, (h) they can control drug release minimizing the development of drug resistance in pathogens or cancer cells [49]. While micro/nanorobots hold immense potential, challenges related to biocompatibility, navigation, and safety in complex biological systems remain. Ongoing research aims to address these challenges and unlock the full potential of micro/nanorobots for revolutionizing drug delivery in pharmaceutical applications.

Conclusion

The advent of micro/nanorobots in pharmaceutical drug delivery promises a transformative leap in the way we administer and benefit from medical treatments. These minuscule machines, designed to operate at the nanoscale, hold the potential to revolutionize healthcare in numerous ways, encouraging further research and innovation in the field. Reports are elated that micro/nanorobots pave the way for personalized medicine. By tailoring drug delivery to individual patient needs, they can optimize treatment regimens, reducing side effects and enhancing therapeutic outcomes. This approach shifts the paradigm from one-size-fits-all to treatments customized for each patient's unique

Table 4 Recent in-vivo studies of nanorobots in pharmaceutical drug delivery

Animal Models	Micro/Nano-robots used	Loaded Drug	Targeted Region	Key Findings	Refs.
Mice	Gold Nanorobots	Doxorubicin (Dox)	Tumor	– Enhanced drug delivery Tumor shrinkage	[51]
Rats	Magnetic Nanorobots	Paclitaxel (PTX)	Bloodstream	– Improved drug circulation Improved efficacy	[52]
Rabbits	Polymer Nanorobots	Methotrexate (MTX)	Joints	– Reduced inflammation Targeted therapy	[53]
Guinea Pigs	Lipid Nanorobots	Insulin	Gastrointestinal	– Controlled insulin release Controlled efficacy	[54]
Monkeys	DNA Nanorobots	Antiviral Drug	Brain	– Enhanced brain drug delivery	[7, 55]

biology. Many diseases, such as brain disorders or certain cancers, are challenging to treat due to biological barriers like the blood–brain barrier. Micro/nanorobots can cross these barriers, opening up new possibilities for treating conditions that were once considered inaccessible. Micro/nanorobots enable multimodal therapies by delivering multiple drugs or therapeutic agents simultaneously. This multifaceted approach can tackle complex diseases from different angles, potentially enhancing treatment efficacy and reducing drug resistance. They are also capable of contributing to reduced drug dosages, precise drug targeting, and minimizing toxicity and side effects. Patients can benefit from more effective treatments with fewer adverse reactions.

Encouraging investment in nanorobotics research, fostering multidisciplinary collaborations, and establishing safety and efficacy standards through regulatory bodies are crucial steps. These efforts will drive progress and pave the way for a healthcare future where treatments are not only more effective but also safer and tailored to each patient's unique needs. In summary, micro/nanorobots represent a promising frontier in pharmaceutical drug delivery, offering the prospect of a brighter and healthier future in medicine through innovation, collaboration, and dedicated research endeavors.

Abbreviations

DDS	Drug delivery system
ABF	Artificial bacterial flagella
CNT	Carbon nanotube
BBB	Blood brain barrier

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Tanisha Das and Shirin Sultana collected and analysed the data. Tanisha Das drafted the paper; all authors have read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethical approval and consent to participate

No ethics approval or consent was required.

Consent for publication

The authors declare no conflict of interest.

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