Nanorobots in Targeted Drug Delivery System – A General Review

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Abstract

A targeted drug delivery system is a method for accurately administering the drug component to a targeted area of the body (such as an organ, cellular level, or subcellular level of a specific tissue), with the goal of avoiding the non-specific adverse effects linked to conventional drug delivery [1]. The presence of targeted drug delivery systems allows the reduction of cytotoxic drugs overall toxicity, reducing side effects, while improving the efficacy and selectivity of the drugs [2]. This strategy eventually leads to a decrease in the amount of medication required to achieve therapeutic efficacy. This method is especially beneficial in the treatment of several diseases, such as cancer, because unlike chemotherapy that often results in the death of all rapidly proliferating cells in order to eradicate tumor or cancerous cells, the majority of targeted therapy approaches work to treat cancer by disrupting particular proteins that aid in the growth and metastasis of tumors in the body [3]. This in turn improves therapy effectiveness and decreases undesirable side effects. Side effects occur as a result of cancer treatment including pain, fatigue, anemia, and hair, skin, and nail problems [4].

The field of study of nanorobotics is an emerging field of study with a revolutionary potential in various areas, including biomedicine [5]. The application of nanorobots in targeted drug delivery systems, especially as therapeutic agents carriers aids in the succession of targeted drug delivery systems. This journal discusses the topic of nanorobots in the Targeted Drug Delivery System, spotlighting its fabrication, applications, limitations, and future direction. In addition, general knowledge regarding nanorobots profile is fundamental in the comprehension of its applications, hence the provision of sections 'Nanorobots profile'.

Keywords: Targeted drug delivery, Nanorobots, Propulsion Type, Pharmaceutical drugs, Top-down and bottom-up approaches, Precision control, Biologics, Biocompatibility, Scalability

1. NANOROBOTS PROFILE

Micro- and nanorobots development stands as a promising field of research, especially in resolving issues related to biomedicine, targeted drug delivery, and more [6]. However, the concept of nanoscale machines, or nanorobots was once thought to only be existent in the science fiction realm some decades ago [7]. The development of nanorobots technology poses numerous challenges. These challenges include technical, biological, physicochemical, and safety concerns relating to the newly used materials and devices at the nanoscale in the body. The term "Nanorobotics" describes an emerging scientific and technological field focusing on the design, development and control of robots at the nanoscale [7]. The size range covered by the nanoscale is 1 to 100 nanometers (nm), in which one nanometer equals one billionth of a meter ($1 x 10^{-9}$ m) [5][8]. Medical nanorobots are untethered nanostructures with engines or the ability to convert various energy sources into mechanical forces to carry out medical tasks [9]. "Due to their small sizes, nanorobots can directly interact with cells and even penetrate them, providing direct access to the cellular machineries." [9]. Nanorobots are designed with an array of technologically advanced components that enable them to function well within the human body, in contrast to conventional nanomaterials, which are generally utilized as drug delivery vessels [9]. It could also be perceived as devices for identifying allies or adversaries; when detecting an adversary, they undergo a conformational shift that triggers the release of a material that can neutralize it [7]. As a new emerging field, the history of nanorobotics is not yet very long.

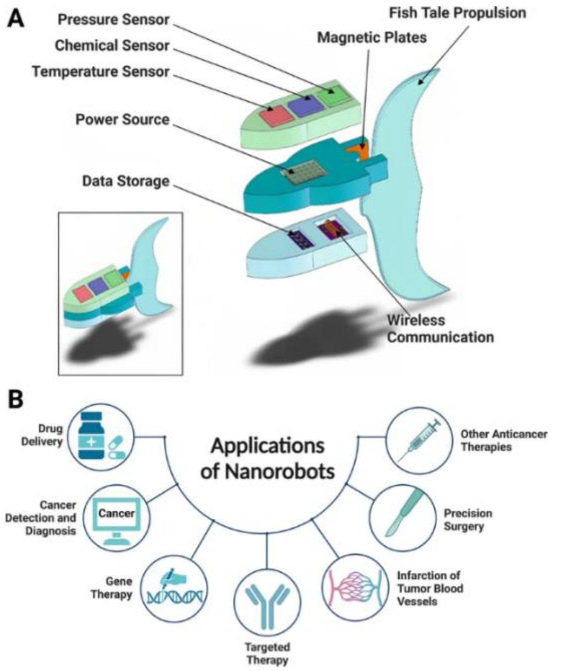


***Figure 1**. Fundamental architecture of nanorobots, including components and applications. (**A**) comprehensive look at a fully operational, self-sufficient nanorobot designed to treat cancer, along with each of its component parts. (**B**) A diagram illustrating how nanorobots might be used to treat cancer. Some nanorobots' components consist of a biocompatible outer shell made of silicon, carbon, or diamond that shields the nanorobot and its internal parts from the surrounding biological environment [9].*

The history of nanorobots, also known as nanobots, started with the mentioning of the term “nanobots” in the lecture “There’s Plenty of Room at the Bottom” by the physicist Richard Feynman in 1959. The lecture discussed the possibility of making things at the atomic level, where Richard Feynman predicted the achievement of such a possibility someday [10][11]. He also made comments regarding the utilization of nano dips and nanobots to cure heart disease. Later, genetically programmable molecular machines were described as emerging technologies in cellular biology in the book "Engines of Creation" written by scientist Eric Drexler, who was inspired by the talk. The first nanobots related study was conducted by Robert Freitas, relating to respirocytes; medical nanobots that resemble red blood cells [7].

Numerous materials, both organic (such as proteins) and inorganic (such as silver and diamond), are able to be utilized in the production of nanobots. Metal such as silver has an advantage of being able to serve multiple purposes: it can be used as the base of a nanobot and has antimicrobial properties. On the other hand, diamond is renowned for its exceptional performance and strength. Room temperature liquid metal gallium-based materials are promising to be used in the creation of nanorobots for targeted drug delivery, however, they are mostly restricted to sub centimeter and millimeter scales, and they face biocompatibility issues due to their large sizes and propulsion methods [12]. Selecting the right materials for nanobots is essential, and current research is concentrated on creating and comprehending these materials' characteristics to produce safe and effective nanobots [7]. The method utilized in manufacturing varies based on what material is being used to make it.

There are several necessary components in the nanorobots, including sensors, power supplies (propulsion), motor, and controller [13][14]. Some other important parts include power supplies and molecular computers. Research on the contribution of nanomotors in drug loading applications has been conducted [15]. There are some parts (devices) needed in order to allow for specific tasks, such as storage compartments or manipulators [7]. One of the primary goals of medical nanobot research has been to create therapies that precisely target the areas of the body that require them, with the goal of reducing the negative effects that conventional treatments have on healthy body parts, such as desired in the case of cancer and/or tumor treatment. In that case, nanobots are designated to mobilize and locate problematic areas, and send feedback (or more). This is where the two parts, sensors and propulsion equipment, become essential.

2. NANOROBOTS FABRICATION

Micro/nanorobot fabrication demands continuous engine operation to generate sufficient force against environmental resistance, requiring diverse functional materials and processing methods. The manufacturing approaches include top-down (e.g., PVD, self-crimping, 3D printing) and bottom-up methods (e.g., electrodeposition, self-assembly), each with unique details. Physical

Vapor Deposition (PVD), involves generating a gaseous state of the plating material, followed by collisions among the atoms, molecules, or ions, leading to various reactions and the deposition of interconnected layers onto the substrate, ultimately forming a film [16]. Template-assisted electrodeposition utilizes a filter membrane stencil with monodispersed microporous structures, serving as reaction vessels for the electrochemical deposition of particles, enabling mass production of micro/nanorobots [17].

Self-assembly relies on noncovalent bonding interactions to organize basic structural units into stable structures. Layer-by-layer self-assembly, a supramolecular technique, creates multilayer membranes through alternating deposition of anions and cations, suitable for permeable membranes and surface modifications [18]. Self-crimping technology utilizes strain differences between materials to preset stress distribution during multilayer material deposition, resulting in spontaneous curling into 3D tubular or spiral structures [19][20]. 3D laser printing enables the creation of intricate 3D micro/nanostructures by processing 2D graphics layer by layer. The process involves converging two laser beams to polymerize molecules, with subsequent PVD deposition of thin magnetic and biocompatible layers [21].

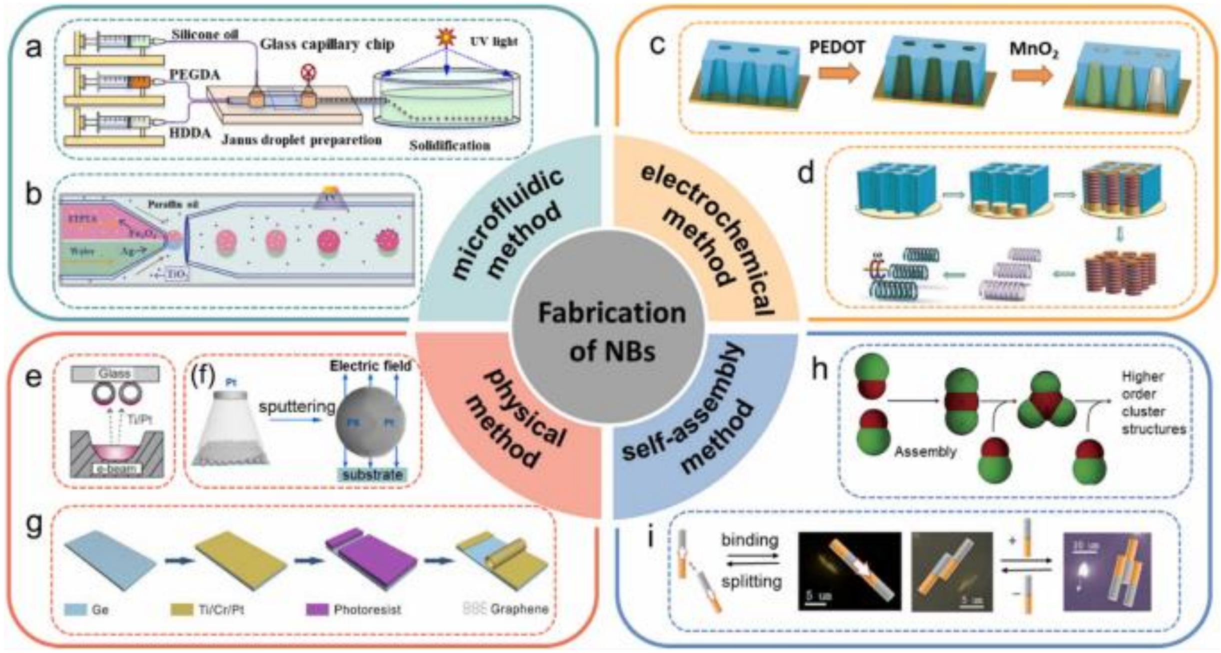


***Figure 2**. Different fabrication methods for micro/nanorobots. (**a**) Microfluidic system schematic for Janus microrobot generation [22]. (**b**) Dispersed phase: Water phase + photocurable ETPTA oil phase with 20 nm Fe3O4 nanoparticles (yellow dots) and modified 50 nm Ag nanoparticles (red dots) [23]. (**c**) Template-assisted electrodeposition of PEDOT/MnO2 micromotors [24]. (**d**) Template-based fabrication of helical magnetic nano swimmers [25]. (**e**) Electron-beam evaporation of Ti/Pt layers on SiO2 microbubbles in vacuum [26]. (**f**) Janus micromotors fabrication by ion sputtering [27]. (**g**) Rolled-up graphene/Ti/Cr/Pt tubular micromotor fabrication [27]. (**h**) Dynamic self-assembly of electrophoretic nanomotors propelling as a cluster in fuel solutions [28]. (**i**) 'Hard–soft' particle assembly forming colloidal molecules and higher-order clusters [29].*

Manufacturing approach	Fabrication Method	Technique	Structure of micro/nanorobots	Material compositions
Top-down	Physical	Physical vapor deposition (sputtering, evaporation, atomic layer deposition), direct laser writing	▪ Yin–yang sphere structures ▪ Helical structures	SiO2, Ag/Cu alloy, Fe/Pt alloy, Cu, Ni, TiO2, Au/Al2O3/Ti/Cu
	Self-crimping	Eroding a sacrificial layer beneath the film, inducing the crimping action.	▪ 3D tubular structure ▪ Spiral structure	InGaAs/GaAs, InGaAs/GaAs/Cr, PEGDA/NIPAAM, NIPAAM, PDMS
	3D laser printing technology	Fused deposition modelling, selective laser sintering, direct ink writing	▪ 3D and 4D structures	SU-8, IP-L, ORMOCOMP, GelMA, PEGDA, PEGDA/PETA, pNIPAM-AAc
Bottom-up	Electrodeposition	Membrane template-assisted electrochemical deposition	▪ Tubular structure ▪ Rod-like structure	Pd, Fe, CoNi/PPy, CoPt
	Self-assembly	Layer-by-layer assembly, macromolecular assembly, shape transformation	▪ Simple structure	PDNBMA/PCzEMA, PVPy/PAA, CaCO3

***Table 1**. Comparison of various fabrication methods for micro/nanorobots [17] [30].*

Nature's intricate mechanisms at small scales, particularly observed in microorganisms utilizing chemical rotors for motion, have inspired the development of synthetic microrobots with diverse rotating structures like helical microstructures, flexible filaments, and tumblers. Departing from traditional magnetic field-driven dragging, these microrobots achieve energetic independence. Various external energy sources power them, including ultrasound, which propels metallic nanowires with standing waves or induces bullet-like motion through the rapid vaporization of chemical fuels [31]. Chemical gradients offer propulsion avenues through self-electrophoresis and bubble propulsion, with a shift towards biocompatible alternatives like enzymes and biodegradable metals such as zinc and magnesium [17]. Enzymes serve as catalytic engines, enabling the use of biomolecules like glucose or urea as fuel [32]. Biodegradable metals react with stomach acid, presenting an appealing option as they degrade after use, leaving non-toxic byproducts [33].

Microrobots can also benefit from optical and electrical fields, although these are less common in biomedical contexts. Biohybrid robots, combining motile microorganisms with synthetic structures, showcase advances in synthetic biology [34]. Genetically engineered bacteria can produce active components like magnetic particles [35], gas-filled microstructures [36], therapeutic payloads [37], or responsive probes [38]. Microrobots fall into two categories based on their powering modalities: locally powered micromotors, equipped with built-in energy conversion for autonomous tasks like microscale mixing, and externally powered microrobots, deriving propulsion from external fields for applications demanding precise control, such as microsurgery or targeted drug delivery [39].

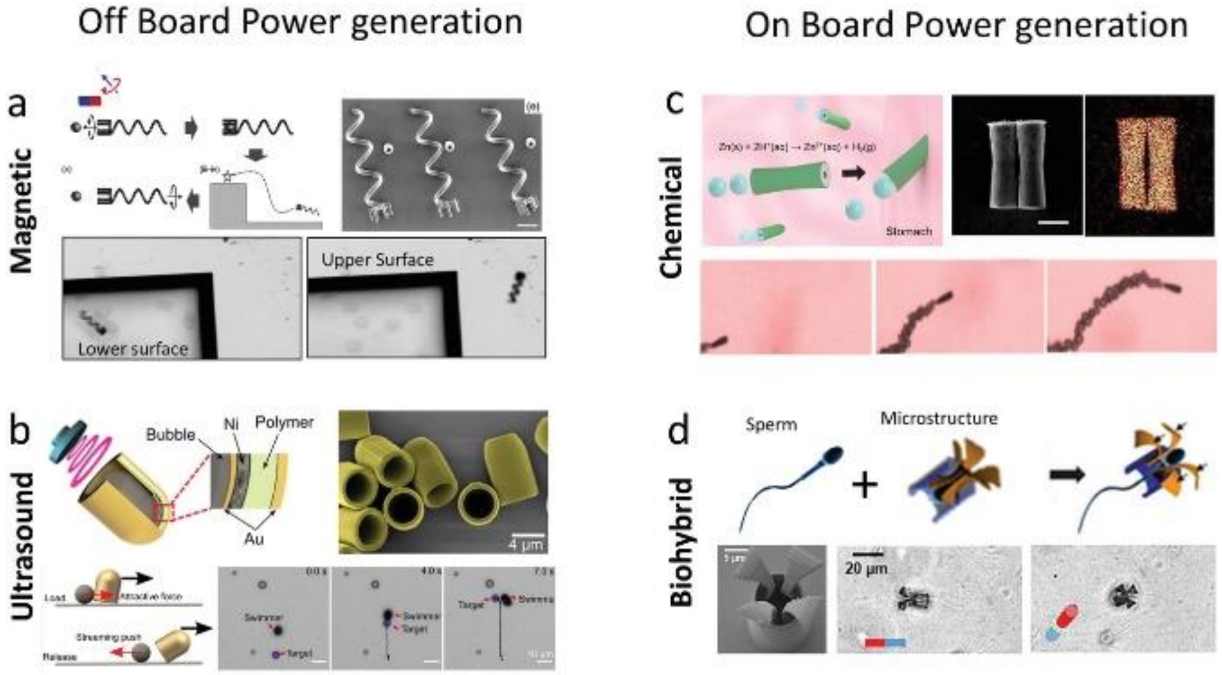


***Figure 3**. Power mechanisms for micro/nanorobots. (**a**) Microrobot propelled magnetically via a rotating micro coil [40]. (**b**) Microrobot propelled by ultrasound, powered through a cavitating microbubble [41]. (**c**) Chemical propulsion system utilizing a zinc microtube; the microrobot transforms gastric fluid into gas bubbles for propulsion [42]. (**d**) Biohybrid microrobot integrating a sperm with a synthetic structure [43].*

3. ADVANCEMENTS IN THE APPLICATION OF MICRO/NANOROBOTS – TARGETED DRUG DELIVERY

The application of nanobots in targeted drug delivery involves the use of micro/nanorobots to precisely deliver therapeutic agents to specific tissues, cells, or subcellular locations, thereby minimizing side effects and maximizing treatment efficacy [*9*][*45*]. Nanobots can be designed to carry and deliver drugs to targeted sites within the body, offering potential advantages over traditional drug delivery methods. For example, chemotaxis-guided hybrid neutrophil micromotors and DNA origami nanorobots have been developed for targeted drug delivery, demonstrating enhanced capabilities in delivering therapeutic payloads to specific locations [*15*] (***Fig. 4***). These nanobots can be propelled by various energy sources, such as magnetic fields, light energy, electric fields, ultrasound energy, and chemical reactions, allowing for precise positioning and controlled drug release [*15*][*46*] (**Fig. 5**) (**Table 2.**). Additionally, the use of nanobots in targeted drug delivery has been explored in animal models, demonstrating their potential to deliver drugs to specific target sites with minimal adverse effects [*15*].

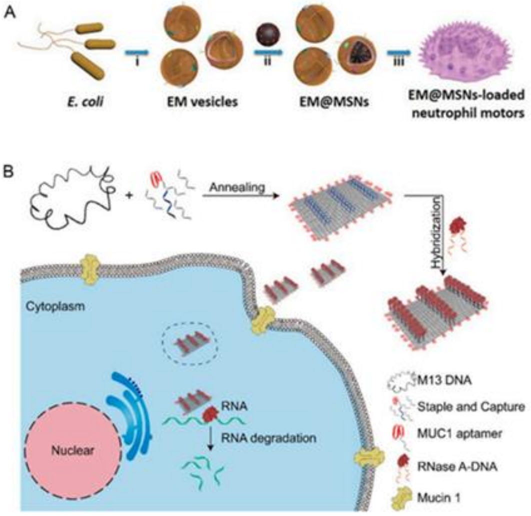


***Figure 4**. (**A**) Chemotaxis-guided hybrid neutrophil micromotor used for targeted drug delivery (**B**) DNA origami nanorobot used for RN [15]*

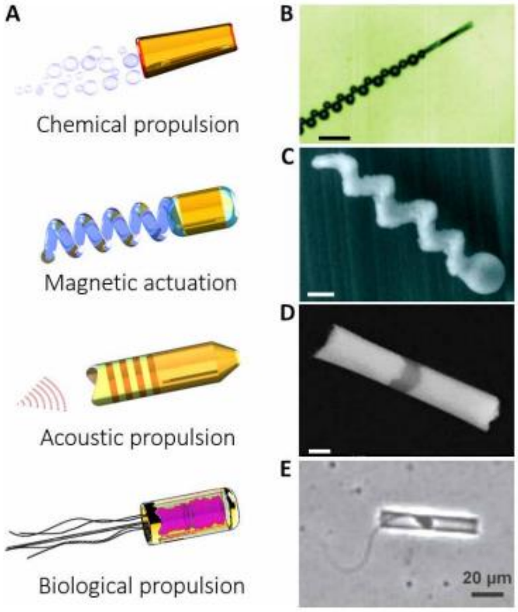
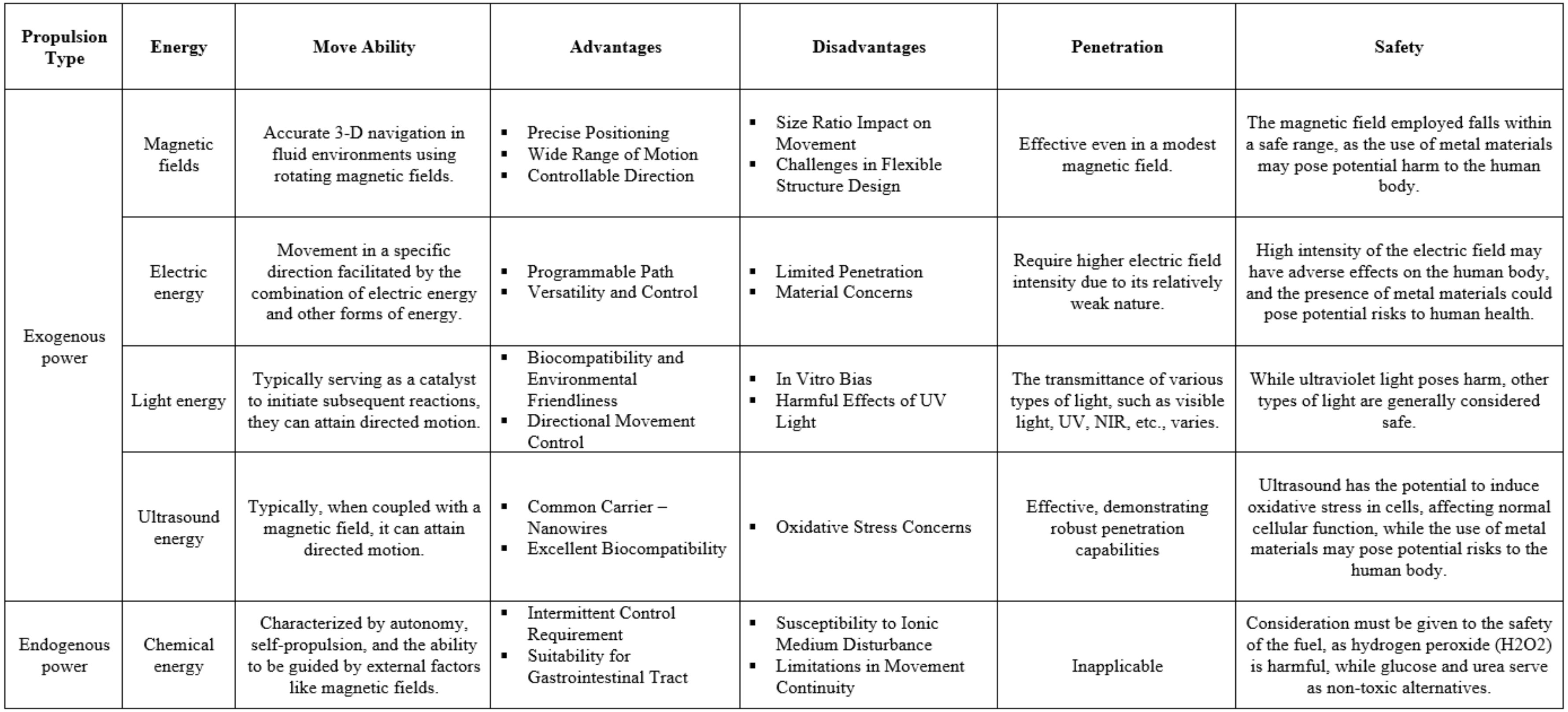


***Figure 5**. Examples of propulsion mechanisms designed to supply energy to micro- and nanorobots (MNRs). (**A**) Common propulsion mechanisms for micro/nanoscale robots. (**B**) Micro rocket powered by chemical reactions. (**C**) Nano swimmer with helical motion actuated magnetically. (**D**) Nanowire motor propelled acoustically. (**E**) Microrobot hybrid propelled by biological means, resembling sperm movement. [47]*

In the realm of contemporary healthcare, two distinct classes of therapeutic agents assume crucial roles in managing diverse medical conditions. These categories encompass a broad spectrum of treatment alternatives, each distinguished by its unique characteristics and applications.



Propulsion Type	Energy	Move Ability	Advantages	Disadvantages	Penetration	Safety
Exogenous power	Magnetic fields	Accurate 3-D navigation in fluid environments using rotating magnetic fields.	▪ Precise Positioning ▪ Wide Range of Motion ▪ Controllable Direction	▪ Size Ratio Impact on Movement ▪ Challenges in Flexible Structure Design	Effective even in a modest magnetic field.	The magnetic field employed falls within a safe range, as the use of metal materials may pose potential harm to the human body.
	Electric energy	Movement in a specific direction facilitated by the combination of electric energy and other forms of energy.	▪ Programmable Path ▪ Versatility and Control	▪ Limited Penetration ▪ Material Concerns	Require higher electric field intensity due to its relatively weak nature.	High intensity of the electric field may have adverse effects on the human body, and the presence of metal materials could pose potential risks to human health.
	Light energy	Typically serving as a catalyst to initiate subsequent reactions, they can attain directed motion.	▪ Biocompatibility and Environmental Friendliness ▪ Directional Movement Control	▪ In Vitro Bias ▪ Harmful Effects of UV Light	The transmittance of various types of light, such as visible light, UV, NIR, etc., varies.	While ultraviolet light poses harm, other types of light are generally considered safe.
	Ultrasound energy	Typically, when coupled with a magnetic field, it can attain directed motion.	▪ Common Carrier – Nanowires ▪ Excellent Biocompatibility	▪ Oxidative Stress Concerns	Effective, demonstrating robust penetration capabilities	Ultrasound has the potential to induce oxidative stress in cells, affecting normal cellular function, while the use of metal materials may pose potential risks to the human body.
Endogenous power	Chemical energy	Characterized by autonomy, self-propulsion, and the ability to be guided by external factors like magnetic fields.	▪ Intermittent Control Requirement ▪ Suitability for Gastrointestinal Tract	▪ Susceptibility to Ionic Medium Disturbance ▪ Limitations in Movement Continuity	Inapplicable	Consideration must be given to the safety of the fuel, as hydrogen peroxide (H2O2) is harmful, while glucose and urea serve as non-toxic alternatives.

Table 2. *Comparison between Micro/Nanorobots Propelled by External and Internal Power Sources [15]*

PHARMACEUTICAL DRUGS

Pharmaceutical drugs stand at the forefront of disease treatment, yet their effectiveness grapples with challenges like poor pharmacokinetic properties, necessitating high dosages and potentially causing side effects. Enter untethered mobile microrobots, particularly nanobots, offering a breakthrough solution. These dynamic microrobots present a novel avenue for delivering precise drug dosages directly to targeted areas, bypassing the need for systemic release of large therapeutic doses [*15*][*39*].

Recent breakthroughs in nanorobot design include the development of 3D printed magnetically powered soft biodegradable structures, capable of tunable doxorubicin delivery. These nanorobots leverage chitosan functionalized photocleavable linkers, facilitating efficient doxorubicin loading and allowing modulation of release kinetics through near-infrared external fields. The integration of natural enzymes, such as lysozyme, enhances safety and biodegradability by effectively degrading the nanorobot structure without generating cytotoxic byproducts. Additionally, gelatin methacryloyl nanorobots demonstrate versatility in drug delivery, utilizing polymer swelling for controlled release. Rolling nanorobots navigate against the bloodstream, detecting target cancer cells with cell-specific antibodies, and induce a near-infrared triggered release of doxorubicin payloads, showcasing potential for targeted drug delivery with minimal cytotoxicity post enzymatic degradation [*39*] (***Fig. 6***).

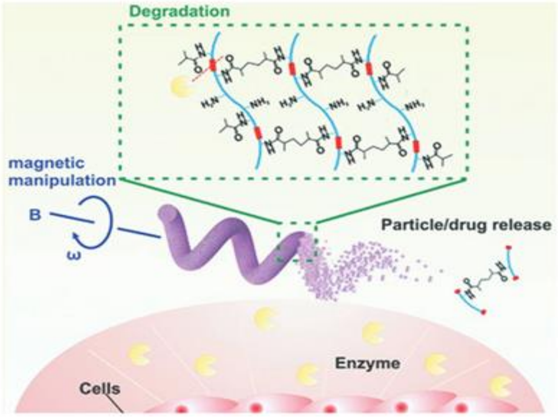


Figure 6. Pharmaceutical delivery through micro/nanorobots: Employing a magnetically powered micro rotor with enzymatic biodegradation to trigger the release of drugs. [*39*]

Delving into the integration of nanobots raises critical considerations about safety and biodegradability. Ongoing research prioritizes the development of nanobots using materials that are both safe and biodegradable [***15***].

BIOLOGICS

Biologics, such as proteins, tissue plasminogen activator, viral vaccines, and antibodies, have garnered significant attention in the field of targeted drug delivery using nanobots. Unlike synthetic pharmaceutical drugs, biologics are therapeutic agents commonly produced by living systems, aiming to utilize compounds already present in the body as active agents. For instance, electrically powered rotor nanobots have been employed to deliver tumor-necrosis factor, demonstrating the capability of a single nanobot to carry and deliver a threshold of tumor necrosis factor to stimulate immune chain reaction signaling inside a single cell.

Moreover, in a recent study, the delivery of Staphylococ-cal α-toxin, a hemolytic factor secreted by Staphylococcus aureus, was successfully achieved using these biomimetic self-propelling nanobots. These nanobots were designed to deliver an attenuated vaccine in mice, with the use of magnesium-based microrobots coated with three layers: a toxin-inserted red blood cell membrane, chitosan, and pH-responsive enteric polymer layers. This approach aimed to detain and neutralize a toxic antigenic payload, promote intestinal localization, and protect oral drugs from the harsh acidic conditions of the stomach, thereby enhancing the efficiency of oral vaccines [*39*] (***Fig. 7***).

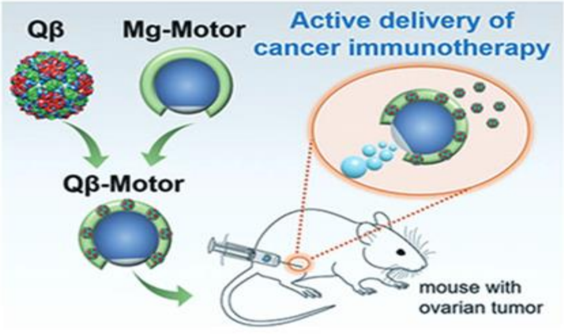


Figure 7. Utilizing micro/nanorobot technology for the delivery of biologics and genes - Employing magnesium-powered micro engines for the administration of virus vaccines in a mice tumor model [*39*]

4. KEY FACTORS RELATES WITH NANOROBOTS AS DRUG DELIVERY SYSTEM

LIMITATIONS OF NANOROBOTS

Nanorobots, with their promise of revolutionizing drug delivery systems, have garnered significant attention in recent years. However, as with any emerging technology, numerous challenges hinder their seamless integration into clinical applications. This journal explores the limitations of nanorobots in drug delivery systems, addressing issues related to energy sources, in vivo operation, smart material integration, and the crucial need for collaboration between nanorobotic scientists and the medical community.

LIMITATIONS OF NANOROBOTS IN PRECISE DRUG DELIVERY CONTROL IN VIVO

Achieving precise control over drug delivery with nanorobots in vivo presents formidable challenges that impede their clinical translation. One critical limitation stems from the feasibility of imaging and tracking within the intricate in vivo environment. While precise monitoring through imaging is imperative, the existing methods may fall short in providing the required resolution and contrast [*48*]. The absence of appropriate in vivo imaging approaches emerges as a significant hurdle, hindering the seamless clinical translation of Micro/Nano Robots (MNR) devices for drug delivery applications.

Another substantial challenge arises from the motion performance of nanorobots in complex body fluids. The in vivo environment, characterized by its dynamic and multifaceted nature, poses a stark contrast to controlled in vitro conditions. The requirement for nanorobots to exhibit improved capabilities, such as precise positioning and directional motion in complex body fluids, becomes apparent [*15*]. However, the current state of nanorobot technology struggles with uncertainty in achieving accurate positioning within the intricate and dynamic in vivo environment. This limitation introduces a significant barrier to the envisioned level of control over drug delivery processes.

The complexity of in vivo environments introduces a layer of uncertainty in the behavior of nanorobots, particularly in the context of their motion performance. The dynamic nature of body fluids, such as blood, presents challenges for nanorobots to adapt and maintain precise control over drug delivery [*49*]. The lack of adaptability to the dynamic in vivo environment hampers the envisioned level of control, making it difficult to ensure the accurate positioning of nanorobots during drug delivery processes and making the nanorobots miss their target cell/tissue. This could lead to negative side effects.

BIOCOMPABILITY AND BIODEGRAD-ABILITY

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One fundamental challenge is the biocompatibility of materials, crucial for nanorobots designed to operate within tumor tissues and cells. The surface properties of nanorobots significantly impact their motion control in biological microenvironments, necessitating materials that are not only biocompatible but also biodegradable. The choice of materials, often biodegradable, ensures the dissolution or disappearance of nanorobots at the end of their tasks[*9*]. Flexibility and deformability are additional requirements to navigate three-dimensional, viscous, and elastic body fluids within the human biological microenvironments effectively.

The propulsion of nanorobots, a vital aspect of their autonomous operation within the body, introduces challenges related to energy sources and locomotion control. Different nanorobot propulsion mechanisms, such as magnetic, ultrasound, and light-driven propulsion, rely on exogenous dynamics, while endogenous dynamics involve chemical or biological reactions [9]. However, the stability of enzyme reactions-driven nanorobots, utilizing bodily fluid constituents as power sources, requires further improvement for practical implementation.

Crucially, the degradation of nanorobots plays a pivotal role in ensuring biosafety. The degradability of materials in nanorobots is essential to avoid post-use operations and potential toxicity concerns. Biodegradable polymers, water-soluble polymers, and natural polymers hybridized with magnetic nanoparticles are explored to achieve controlled degradation, enabling nanorobots to deliver payloads continuously while gradually degrading in the biological system. The potential limitation is significant, as it introduces the risk of accumulation over time. Failure to ensure efficient degradation may lead to chronic inflammatory reactions, emphasizing the need for comprehensive strategies to safely clear micro/nanorobots from the body.

SCALABILITY

Nanorobots in drug delivery systems have shown great potential for targeted and precise delivery of therapeutic agents. However, one of the major challenges associated with nanorobots is scalability. The production of nanorobots in large quantities is a challenging task, and the method of nanoparticle production depends on many factors, including the intention of use, reproducibility of size, size distribution, targetability, and functionality of developed nanoparticles [50]. As the field of nanorobotics continues to advance, addressing the scalability issue will be crucial for the safe and effective use of nanorobots in drug delivery and other biomedical applications.

ADVANTAGES OF NANOROBOTS

Nanorobots have emerged as a groundbreaking technology with the potential to redefine drug delivery systems. Their ability to navigate biological environments with precision and deliver therapeutic payloads directly to target sites holds immense promise for advancing the field of precision medicine.

PRECISE

One of the primary advantages of nanorobots is their unparalleled ability to achieve targeted drug delivery. Through sophisticated navigation systems and surface functionalization, nanorobots can pinpoint specific cells or tissues, ensuring the therapeutic agent reaches its intended destination with remarkable precision. This targeted approach minimizes collateral damage to healthy cells, enhancing the overall efficacy of drug delivery [47]. The precision afforded by nanorobots significantly reduces side effects associated with conventional drug delivery methods. By selectively delivering therapeutic payloads to diseased cells or tissues, nanorobots spare healthy surrounding areas from exposure to the drug. This targeted approach minimizes adverse reactions, offering a substantial advantage in terms of patient safety and treatment tolerability.

MULTIFUNCTIONALITY AND PAYLOAD CAPACITY

Multifunctional nanorobots in drug delivery systems offer a paradigm shift in the field of medicine, providing a versatile and efficient platform for targeted therapeutic interventions. The advantages of these sophisticated nanorobots extend across various dimensions, presenting a promising outlook for the future of drug delivery.

Nanorobots exhibit multifunctional capabilities beyond drug delivery [51]. Their multifunctionality enables precise positioning, controllable direction, and a wide range of capabilities, which are crucial for targeted and effective drug delivery. Furthermore, nanorobots boast impressive payload capacities, allowing for the delivery of diverse therapeutic agents simultaneously. This multifunctionality enhances their utility in comprehensive disease management.

Moreover, multifunctional nanorobots exhibit a remarkable ability to carry diverse payloads concurrently [45]. This multifaceted cargo-carrying capability allows for a combination of therapeutic agents, such as chemotherapy drugs, antibodies, or gene therapies, to be delivered simultaneously. This synergistic approach can address multiple facets of a disease, improving treatment outcomes and potentially overcoming drug resistance, a significant challenge in conventional drug delivery.

FUTURE DIRECTION OF NANOROBOTS

The development of nanorobots will continue to undergo significant advancement, gaining the capability to execute a more diverse range of medical functions and tasks [*9*]. However, in order to develop robust nanobots and advance further, the current challenges and limitations faced needed to be addressed. As discussed in the previous section, the challenges of nanorobots encompass issues such as precise control over drug delivery, ensuring biocompatibility and biodegradability, along with the imperative of scalability. Ensuring precise control, biocompatibility, and biodegradability is imperative to guarantee the optimal safety and efficacy of nanorobots. Nanorobots' construction and control become key challenges in developing nanorobots, because unlike what is encountered by conventional components, nanorobots need to function within a microenvironment of distinct properties [*9*].

Among other methods, precise control may be improved through biological mimicry and swarm-intelligence. Biomimicry and nanotechnology Integration has shown encouraging outcomes in the fields of medicine, robotics, sensors, photonics [*52*]. The emulation of natural structures, designs, and elements with a prospect of developing novel devices with the desired functionalities is termed as Biomimicry [*52*]. In order to achieve precise control, high mobility, deformable structures, sustainable and adaptable processes, swarm-intelligent collective behavior, complex functionality, and even the capacity for self-evolutionary and self-replicating, future nanorobots should strive to emulate the natural intelligence of their biological counterparts [*9*]. This will enable improved therapeutic efficacy and better adaptation to the human body. Biomimicry may also improve biocompatibility and biodegradability [*53*].

The advancement of artificial intelligence (AI) has been recognized as a major advantage for pathologists and radiologists all across the globe [*54*]. Such advancement may also be applied in the improvement of targeted drug delivery systems. Swarm intelligence (SI) is a type of artificial intelligence that uses natural behavior as inspiration to address optimization issues [*55*]. To improve their precision treatment capabilities, the advancement of nanorobot swarm intelligence toward group motion planning, machine learning, and AI toolbox at the nanoscale is critical. In complex biological ecosystems, this will allow for more coordinated behaviors and better adaptability [*9*]. In the near future, emergent systems research could lead to the production of self-organized cell-sized nanobots or independent microrobots swarms that can cooperate in intricate formations without a pilot [*56*]. Furthermore, the utilization of swarm intelligence nanorobots may increase scalability through its efficiency [*57*].

5. CONCLUSION

In conclusion, this journal discusses the importance of nanorobots in targeted drug delivery systems, highlighting the fabrication of nanorobots, its applications, challenges, and future prospects. The field of nanorobotics has a huge potential in various fields, including biomedicine. The ability of nanorobots in the drug delivery system may be accredited to its distinct properties, construction, control, and design, including its fabrication. Diverse functional materials and processing methods are required in the fabrication of micro/nanorobot as continuous engine operation is demanded in order to generate enough force against environmental resistance. Both top-down and bottom-up approaches are included in the manufacturing of nanorobots.

The application of nanorobots in targeted drug delivery is highly beneficial, as it may address some of the challenges possessed by conventional drug delivery. Through the use of micro/nanorobots, precise delivery of therapeutic agents to specific targeted tissues, cells, or subcellular locations can be achieved, and in turns, side effects are minimized, while treatment efficacy is maximized. This is especially crucial in cases where treatments need to precisely function on only a specific location, otherwise it becomes harmful to the body (healthy cells), such as in the case of cancer treatment. Examples of nanobots applications, chemotaxis-guided hybrid neutrophil micromotors and DNA origami nanorobots, have previously been mentioned, in section **'Targeted drug delivery'** for these nanobots to site precisely and control drug release, various energy sources including magnetic fields, light energy, electric fields, ultrasound energy, and chemical reactions, can be used to propel the nanobots. The comparison between each of the energy types is shown by table '**Table 2**' Through the application of nanorobots on the two therapeutic agents classes of contemporary healthcare, pharmaceutical drugs and biologics (with their own advantages and disadvantages), a more effective drug delivery system can be achieved.

However, as the nanorobots need to operate in a unique microenvironment of the body; therefore, the development of nanorobots poses some limitations and challenges. As covered in section…the key limitations include precision control, biocompatibility and biodegradability, and scalability. A critical limitation in the area of precision control over drug delivery with nanorobots in vivo arises from the viability of in vivo tracking and imaging, as current imaging techniques may be inadequate in offering the required resolution and contrast. In order to allow safe and effective utilization of nanorobots within complex biological microenvironments, nanorobotics need to obtain biocompatibility and degradation characteristics. The limitation regarding scalability is associated with the challenges in mass production of nanorobots. Through understanding its limitations, newly improved designs can be explored and developed. Such designs might incorporate biomimicry and swarming-intelligence behavior in order to tackle the challenges and limitations.
Nanorobots have shown to have outstanding performance and potential applications in different fields. The aim for future research should lead to the better performance of nanorobots, as there are certain key criterias needed to be met in order for nanorobots to enter clinical practices [***58***][*9*]. Exploration of nanorobots' application in biological and medical domains should also be aimed in future research [***58***].

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