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Micro/Nanorobots In Drug Delivery: A Review of Advances

Miss. Sanika Vijay Awachar[1], Mr. Santosh Waghmare[2], Dr. Shivshankar Digambar Mhaske[3], Miss. Anisha Keshav Awchar[4], Mr. Om Eknath Avhale[5], Mr. Radheshyam Jawansing Azade[6], Miss. Vaishnavi Dattatray Changade[7].

Satyajeet College of Phamacy, Mehkar

ABSTRACT

Many developments for effective drug delivery have resulted from the last few decades' progress in the drug delivery system. Both micro and nanorobots are thought to be better medication delivery methods since they convert different types of energy into motion and propulsion. Additionally, because it targets specific locations beneath physiological settings and circumstances, it may be beneficial. It has been confirmed that they can encapsulate, transport, and deliver therapeutic ingredients straight to the illness sites, improving therapeutic efficacy and reducing harmful medications' systemic side effects. This overview covers the varieties of micro and nanorobots, their involvement in medication delivery, their biological applications, and their use in illness diagnosis and management

Keywords : micro/nanorobot, targeted drug delivery, drug release, magnetic field ,drug delivery

Introduction :

The ability of humans to recognise, relate to, operate, and modify many systems across the globe has been greatly enhanced by robot systems. The coming together of different technologies.Technologies have transformed a number of industries, most notably robotics for therapeutic applications to improve healthcare.[1] Therapeutic robot devices are created specifically for the diagnosis of diseases, whereas industrial robots were primarily developed to mechanise predictable and dangerous macroscale produced liabilities.disease diagnosis and treatment. Therefore, the therapeutic robots demand fewer sections and insolent resources for intricate and thorough treatments, as well as improved reproducibility in the human body, in contrast to conventional (old) robots, which are fictionalised by enormous mechanical systems. Technological developments including the merging of control theory, motors, components, and medical imaging have produced impressive strides in medical robotics, as seen by the increase in surgeon-patient acceptance.[2] For example, da Vinci surgical robot systems allow the surgeon's hand movements to be converted into precise, tiny movements of tiny devices inside the patient's body. Even though robotic systems are widely used for minimally invasive surgery, the most common mechanical issues and duties still exist.[3] Robots have become a viable alternative for the regulated and targeted distribution of medications. Robotic devices' regulated, accurate, and site-specific medication administration capabilities are their primary advantage.ability, in contrast to other smaller, traditional medicinal delivery methods. In addition to being able to target specific single cells, robots such as stimuli responsive and surface-functionalized magnetic helical microswimmers may also target the appropriate regions of the tissues for the precise and controlled distribution of medicines, genes, or cells[4] In small robot-like (micro/nanorobots), the process of cargo/drug release is often triggered passively through restricted physiological environment alterations.conditions (such pH and temperature) at the intended location. However, complicated physiological settings or unexpected local differences may result in the delivery of potential off-target therapy. Therefore, creating an assimilated mobile robot (micro/nanorobot) that can be triggered superficially will provide a sufficient amount that is both manageable and satisfactory.[5] For mobility and on-demand triggered treatments, a therapeutic delivery platform should ideally independently and cooperatively utilise an equal external power supply. However, the inter While using the same amount of energy, the action between these two tasks is thrilling.[6] New technologies emerge more quickly as a result of the quick development of fields like materials science, molecular biology, mechanical dynamics, artificial intelligence, and others. Nano/microrobots entered scientists' thoughts more and more. In 1959, Richard Feynman made the first suggestion for the application of microrobots in medical therapy. At that point, the word "nanorobot" was created. As a developing technology, micro/nanorobots have been widely used in the medical field for activities like drug/cell delivery, medical diagnostics, and auxiliary operations. Unlike the traditional method of medication delivery, which relies on blood flow to reach the target, micro/nanorobots may be able to achieve autonomous mobility, enabling us to administer controlled nanoparticles to difficult-to-reach areas.[7] Current developments in the classification, use, and delivery of drugs, targeted medication delivery, and other medical applications of micro and nanorobots are covered in This article.

Classifications of robots :

1. **Microrobots :**

Microrobots have shown significant promise in carrying out a number of crucial tasks, such as drug delivery, cell manipulation, microassembly, and biosensing through manual systems[8] For instance, magnetotactic bacteria were exhausted under DC magnetic field gradients to establish tailored delivery. [9] Numerous researchers have demonstrated that microrobots can use magnetic fields to move target materials like chemicals and cells. Additionally, micro grippers have been developed. for microrobots employing a special system called micro-electromechanical systems, a technology that might be used to increase the functionality of microrobots. The established microrobots' kinematic models were designed with motion control in mind. The microrobots, both biological and non biological, have been guided via autonomous motion planning.[10] Other therapeutic immersion tools besides theranostic ones may be used in teleoperated microsurgery. For example, microrobots can be used for rotational therapy and thrombolysis. atherectomy to remove blood clots and inscriptions in order to restore blood flow to the injured aorta or other blood vessels. Angiogenesis is the process by which both benign and malignant tumours create new blood arteries, attach metastatic cancer cells to small, isolated regions, and create a circulatory network.[11] By using milli/microrobots to specifically identify the signs of malignant tumours (metastasis and angiogenesis), the angiogenic tree can be blocked at its base to expel the vascus.distant organs by supplying and halting the passage of cancer cells.[12] Additionally, the angiogenic system could be used at a precise body targeting location to deliver milli/microrobots that are laden with diagnostic tools including imaging agents, chemotherapy, and radiation therapy. genetic agents (mRNA and DNA), or substances like medications, proteins, and radioactive seeds [13] Remote opto-magnetics or heating switches can be used to trigger the release of therapeutic ingredients.[14] Microrobots or milli may be used to scatter radioactive nucleoids for brachytherapy, which uses the source of radiated energy at the core of the tumour to eradicate the tumours.[15]

2. Nanorobat :

his kind of nanodevice is used to control or protect against human infections. It is a tiny tool designed to accurately complete a certain project or sporadic duties. at 1–100 nm nanoscale

proportions. They can carry out their duties at the therapeutic and industrialised levels because they are predictable to strength at three distinct atomic, molecular, and cellular levels.[16] Since nanorobots are microscopically small, as stated in nanorobotic theory, "it would likely be necessary for very huge numbers of them to operate together to execute microscopic and macroscopic activities [17] The creation of intelligent nanorobotic drug delivery systems could result from advancements in robotics engineering, computers, medications, nanotechnology, and bioinformatics. tems. There are several types of nanorobots, including cellular repair, microbivore, surgical, and respiratory cell nanorobots.

The purpose of these nanorobots is to defend and shield the human body from pathogens. Their width ranges from 0.5 to 3 microns, and they are made with proportions in Nanometres vary from 1 to 100. Because of its strength and inertness, carbon is most frequently used in nanorobots in the forms of diamond and fullerene.[18] The external passive diamond coating on nanorobots is designed to shield them from immune system attacks. Because they are It is challenging to manipulate and work with them because they are invisible to the human eye. Techniques like Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM) are being utilised to identify the molecular structure of these nanoscaled robotic systems. In biotechnology and nanoscience, virtual reality (VR) techniques are now being developed to increase operator awareness by predicting additional or less positions of "full immersion" or "telepresence." [19] The two most challenging parts of creating nanorobots or nanomachine components are their construction and control. These gadgets will work. in microenvironments that differ from standard components in terms of their physical properties. To accomplish this shared goal, the area of nanorobotics necessitates a multidisciplinary approach from biologists, physicists, engineers, computer scientists, chemists, and other experts. Although this subject is still developing, seasoned researchers have made several thoughtful moves that are advancing this fascinating and engaging field.[20]

Computer controlled micro and nanorobot :

1.Pharmacyte :

Pharmacytes are medicinal nanorobots that have a diameter of 1-2 lm and can hold drugs in reservoirs up to 1-3 lm. They are arranged for classification pumps. and controlled, using mechanical mechanisms. They are delivered by chemotactic sensors or molecular markers, which guarantee the targeting system's accuracy. Power, glucose, and oxygen are collected from the restricted environments, including intestinal fluid, blood, and cytosol. After completing the duties, nanorobots can be eliminated or recovered via centrifuge nanopheresis. [21]

2.Microchips :

Human molecules overlap microchips found in nanorobots, and when the molecules identify a sickness, the chip transmits electrical signals. As an illustration, the unique sensor nanobots may anticipate illnesses, authenticate blood contents, and be administered through the blood beneath the skin. Additionally, they can be used to report blood sugar levels. The advantages include being easy to use and having a little yield charge.[22]

3.Respirocyte :

This particular kind of nanorobot functions similarly to an artificial red blood cell in carrying oxygen. Endogenous serum glucose is used to generate the power. These synthetic cells have the capacity to supply 236 times more oxygen to the tissues per unit volume as opposed to direct acidity and red blood cells (RBCs).[23]

4.Microbivores :

With a diameter of 3.4 lm along its major axis and 2.0 lm on its minor axis, this device is spheroidal and flat for application in nanomedicine.[24] Its phagocytic ability, which is over 80 times more proficient than that of other macrophages in terms of (volume/sec digested) per unit vol, is another distinctive feature. amount of a phagocytic substance[25]

5.Clottocytes :

Clottocytes, also known as artificial mechanical platelets, have a unique biological feature that allows for "instant" haemostasis.Additionally, platelets are blood cells that are roughly spherical and lack a nucleus, which is around two millimetres in size, adheres to a bleeding site and aids with clotting blood vessels to halt the bleeding. Additionally, they carry materials that aid in the coagulation process. [26]

6.Chromallocyte :

In order to combat ageing, chromallocytes would replace entire chromosomes in individual cells, fixing genetic flaws and other long-term harm to the genetic composition. Within a cellular machine will initially evaluate the state by examining the structural components, behaviours, and activities of the cells. These repair devices may completely redesign a cell, both structurally and molecule-to molecule.[27]

Micro and nanorobots in drug delivery :

The development of micro- and nano-electromechanical systems has made it possible to create implantable robots that can carry out a variety of tasks, including the trolled the delivery of drugs and DNA. Because of the tremendous gains in nanotechnology, considerable emphasis has been directed to developing nanorobots outfitted with an internal or external power source, sensors, and artificial intelligence (AI). When compared to conventional therapies, these intelligent systems are more effective and have fewer side effects because they are skilled at information processing, signalling, sensing, actuation, and communication. They can also carry out biological functions at the cellular level and deliver medications locally. Navigation, collision avoidance, target identification, detection and attachment, drug delivery, task completion, and other rules make up the bionanorobot rule structure. activation guidelines for the self-closing mode that lead to bionanorobot excretion. In smart molecular manufacturing, the use of AI enables Controlling the behaviour or mobility of nanorobots [28] Drug delivery systems based on nanorobots or nanorobot-based collaborative and autonomous behaviours have been effectively simulated by modelling and simulation techniques [16]. After intravenous delivery, bionanorobots are released into the bloodstream, where bioactuation mechanisms help them swim and swarm. Novel forms of controlled drug delivery devices for targeted therapy in a range of disorders, particularly chronic ones, have been proposed, including wirelessly controlled and highly penetrable microrobots, swimming microrobots for controlled drug delivery, and transient microrobot systems for targeted drug delivery using touch or nano-communication frameworks. [29] Social behaviour, emotional perception, and verbal communication are all problematic for kids with autism spectrum disorders. They struggle to build relationships in society as well. They are unable to read people's body language, make eye contact, or communicate their emotions. Since there is currently no cure for autism in children, the only way to improve their quality of life is to provide them with stable social environments[30] Numerous therapeutic modalities have been developed, such as animal-assisted therapy and robot-assisted therapy. Robot-assisted therapy has been found to has a benefit over therapy with animals since robots are simpler to operate. It prevents illness and animal sensitivities.[31] Libin et al. explained the guidelines for creating a communicative artificial creature; a plating game aids in education and the administration of therapeutic drugs to people of all ages. It is capable of communicating engage with a patient on a variety of levels, including social, cognitive, tactile-kinesthetic, emotional, and sensory. Both verbal and nonverbal communication are possible.[32]

In addition to its usage in autism, robots have other applications, which are listed below.

1. Long-term care setting: Robots perform nursing services, such as nursing care and related services to treat the sick, injured, and disabled, in long-term care settings. People with disabilities.

2. Short-term inpatient hospital: Robotics technology can be used in hospital areas that offer diagnosis and therapy services (both surgical and non-surgical), where patients are admitted for treatment under a doctor's care.

3. Short-term urgent care facility: A clinic or office space intended to identify and treat ambulatory persons in need of rapid medical attention for illnesses or injuries medical Attention.

4. Shorter term hospice: Area other than the patient’s residen tial area, where supportive and palliative care is provided for critical patients by the robots.

5. Home care: Robots may be able to provide patient care outside of a hospital setting, at a patient's private residence.[33]

Micro and nanorobots for targeted drug delivery :

The strength and direction required for local delivery and deep penetration outside of their flaccid size are lacking in current micro/nanocarriers drug delivery, which relies on systemic administration. to limitations in transportation. Drug carriers are expected to have extraordinary characteristics, including controlled navigation, driving force, payload, release, and ultimately penetration into the tissues, in order to achieve accurate therapeutic delivery to precisely impacted locations.[34] Micro/nanorobots are a new and intelligent class of drug carriers that may meet these needs, even though these trials are yet unfulfilled for current drug delivery systems (DDS). The motor-like micro/nanorobots can swiftly move and deliver therapeutic payloads straight to the illness site, improving therapeutic efficacy and reducing the systemic side effects of extremely hazardous medications.[35]

micro/nanorobots based on bacteria, red blood cells, or stem cells are thought to be effective and compatible for the targeted delivery of drugs. Cells and microorganisms have a good escape mechanism and are biocompatible, which may be passed to micro/nanorobots that aid in targeted drug delivery. However, covering the cell membrane reduces environmental recognition but does not enable directed movement, requiring external mag netic fields, sound waves, or other stimuli Mesoporous silica nanoparticles (MSNs) and chemotactic neutrophils were combined to create self guided hybrid micromotors by Shao et al. Because of The created system was able to effectively move along the chemoattractant gradients produced by E. coli because they were pre-coated on MSNs loaded with Dox. [36] When driven by ultrasonic energy, magnetic nanoparticles (MNPs) contained within red blood cells (RBCs) offer efficient magnetic control and movement. The RBC microrobot has the ability to move and transport medications along pre-established pathways after being loaded with MNPs, quantum dots (QDs) imaging agents, and doxorubicin (Dox). Additionally, compared to Dox and QDs alone, its cytotoxicity was three times lower. Additionally, magneto-aerotactic microorganisms are frequently used. When Magnetococcus marinus strain MC-1 was combined with drug-containing nanoliposomes, Felfoul et al. discovered that more than 55% of cells were able to enter the targeted tumour hypoxic zones and administer the medication. It is worthwhile to look into the movement characteristics and behaviours of a variety of microorganisms and cells in vivo as possible targets for future nanorobot imitation. The delivery function and purpose of such micro/nanorobots in in vitro laboratory settings have been confirmed by numerous preliminary studies. Wu et al., for instance, detailed the creation of a multi Doxorubicin was encapsulated by a layer-by-layer assembly of a tubular polymeric nanomotor using a porous membrane template, and the nanomotor effectively delivered the drug to the cancer location.[37] Ma et al. created a chemically powered Janus-nanomotor that enabled a 100% dissemination improvement and functioned as a nanoscale drug carrier.compared to a forceless, passive targeted system[38] Likewise, Mou et al. created a magnesium-based, biocompatible Janus micromotor that demonstrated well-structured autonomousshowed temperature-triggered drug release and mobility in blood plasma (devoid of extra fuel) and mimicked bodily fluids.[39] Gao et al. created a magnetic micromotor carrier to deliver drugs to HeLa cells at particular sites using magnetic polymeric particles. [40] Additionally, Walker et al. have developed enzymatically active magnetic micro propellers that have the potential to effectively penetrate mucin gels. [41] Additionally, Garcia-Gradilla et al. confirmed that light stimulated release using ultrasound-driven nanowire motors could deliver drugs to cancer cells quickly. Currently, a magnetic field is used to induce the release of a medicine in hybrid magnetoelectric nanorobotics, which is designed for targeted drug delivery.[42]

Micro and nanorobots in active drug targeting :

Thanks to decades of persistent research, micro and nanorobots for active medication delivery have progressed from test tubes to cellular and vivo animal models. Right now, Several methods, including as physical adsorption, layer-by-layer (LbL) encapsulation, and electrostatic coupling, have been developed for loading model medicines into micro-/nanorobots. To guide drug-loaded micro- or nanorobots to a predetermined site, magnetic fields or disease-linked biochemical gradients are typically employed. Once at the destination, the release of encapsulated therapeutics may be triggered by external fields (such as ultrasound, near-infrared light, and magnetic fields) or physiological circumstances (such as pH). In vitro active medication delivery using chemically/biochemically driven micro and nanorobots has been thoroughly studied, with notable advancements made recently.[43] The first catalytic nanorobots for medication release and transportation were developed, according to Wang and colleagues. The Ni/(Au50/Ag50)/catalytic Through magnetic interactions, Ni/Pt nanowire robots may be able to grasp the drug carriers contained in Fe_3O_4. The homogeneous magnetic fields (H) have the ability to take, transport, and distribute drug carriers of various sizes at predetermined sites. However, because self-electrophoresis powers these nanowire robots, they are unable to function in environments with high ionic strength. [44] In contrast, efficient mobility in physiologically relevant fluids is made possible by bubble-ejected micro and nanorobots. Wu and colleagues reported the development creation of a medication delivery device using a tubular polymeric nanorobot. This tubular polymeric nanorobot's multilayer wall was coated with magnetic Fe_3O_4 nanoparticles, catalytic Pt nanoparticles, and the fluorescent anticancer medication doxorubicin (DOX). The nanorobot can travel and steer itself to designated cells in an H_2O_2 solution under H. The accompanying differential interference contrast image showed that the nanorobots encased in DOX were attached to the outer surface of the HeLa cells. surface. The corresponding confocal laser scanning microscope photos showed almost no fluorescence from the DOX in the nanorobot after ultrasound irradiation, indicating that the majority of the DOX molecules were released during the ultrasound irradiation.[45]

Micro and nanorobots overcomes limitations of passive targeted drug delivery :

The power and navigation required for targeted distribution and tissue penetration beyond their passive mass transport limits are absent from current micro/nanocarriers, which rely on blood circulation. Drug delivery vehicles should have a number of unique features, including as tissue penetration, controlled navigation, cargo conveyance and release, and pushing power, in order to deliver therapeutic payloads exactly to disease areas. Although these issues still plague current therapeutic delivery techniques, micro/nanorobots present a new and exciting class of drug carriers that can accomplish these intended outcomes. Motor-like micro/nanorobots have the ability to move swiftly and deliver therapeutic payloads straight to sick locations, enhancing therapeutic efficacy and reducing systemic side effects linked to potentially dangerous medications. Furthermore, systemic chemotherapy typically targets both tumours and certain healthy cells, making it non-specific. In order to address concerns about systemic toxicity, more work is being done to provide more specialised treatments. Two primary approaches that aim to induce tumor-specific effects include systemic medications, which solely affect cancer cells, and pharmaceuticals that are selectively delivered into the tumour cells and/or associated microenvironments in order to address the inadequate targeting of conventional therapies. [46] The first strategy exploits the altered biological characteristics of cancer cells, which encourage carcinogenesis. Synthetic lethality is the term for the phenomena whereby these changes may make cancer cells more dependent on biological pathways that, if targeted, kill them with very little damage to healthy cells. Now, a few of these techniques have obtained clinical approval. However, they are limited by tumour heterogeneity and drug resistance, and they only help a very small percentage of cancer patients.[41] Therefore, strategies for the second technique—

such as cancer targeting, enhancing medication half-life, and encapsulating drugs in nanoparticles—are needed. However, these nanomedicines have not been very successful, probably because they rely on diffusion and the patient's blood flow for distribution, which limits their ability to enter and aggregate inside tumours, particularly the hypoxic tumour cores, which are challenging to treat. Active transport aims to improve the drug's diffusion to targeted regions by employing self-propelled nanoparticles, often known as nanomotors or nanorobots. In a perfect world, they would be able to cross flows and go to places like high viscosity where drug diffusion is limited or the medications cannot penetrate. [16] The limitations of currently existing passive nanomedicines can be effectively addressed by microrobots. These tiny deviations, which range in size from 0.1 to 100 mm, have the ability to target cancers more aggressively and directly since they can transcend diffusion. Microrobots may be made to enter thick, malignant, and healthy tissues, in contrast to passive nanoparticle drug transporters. Additionally, they might have sensory abilities that can recognise and aid in the growth of cancer cells in their chemical milieu. Microrobots may be made to not only carry and distribute medications with high spatiotemporal accuracy, but also to shield their payload from being diluted by body fluids.[7] Self-propelled micro/nanomotors were used in several proof-of-concept studies to carry anticancer medications, and once the micro/nanomotors arrived at the in vitro target cells, more anticancer chemicals were released.Similar to this, micro/nanorobots were evaluated in vivo; these devices are anticipated to develop into powerful active-transport vehicles that could enable a variety of therapeutic uses that would otherwise be unfeasible with the current passive delivery techniques.[47]

Micro/Nanorobots with Autonomous Movement Ability :

The drug delivery robot system must overcome Brownian motion in order to achieve autonomous mobility in complex bodily fluids because it is only micro or nanoscale in size. The behaviour of the micro/nanorobot is often controlled and coordinated by an exogenous power source in order to propel particle movement. Drug carriers commonly use electromagnetic fields, electric fields, light energy, acoustic waves, and heat energy as external powers. Several driving modes are frequently combined during the actual design process to create micro/nanorobots with multiple purposes.

1. Electric Field Propelled Micro/Nanorobots :

in most cases, magnetic and electric energy cannot be separated, yet in some situations, they can change one another. The micro/nanorobot powered by an electric field is also widely used. There have been reports of a Janus colloidal system powered by magnetic and electrical energy.[48] an external high frequency electric field (0.5–2.5 MHz) allows the metal dielectric Janus colloidal system to travel autonomously and pick up cargo. Because the Janus colloid's hemisphere was covered in a layer of nickel, a magnetic field could be used to guide its movements. This allowed the micro/nanorobot's course to be programmed, enabling precise cargo delivery. Rahman et al. created a carbon nanotube rotating nanomotor construction that demonstrated quick response times and extremely high speed movement in an electric field.[49] The electric-induced water dipole orientation was the source of the motion, but it only demonstrated favourable properties in water; its effects on replicating bodily fluids or more intricate human systems were unknown. Additionally, under the combined effects of light energy and electric fields, nanoparticles can migrate in a certain direction.[50]

2. Light Energy Propelled Micro/Nanorobots :

Another popular technique that has shown excellent controllability and programmability is light energy, which is mostly employed as an auxiliary means. Modulating the light's frequency, polarisation, intensity, and propagation direction allows the nanorobot to move in a certain direction. Zhan et al. created an artificial swimmer by combining two cross-aligned dichroic nanomotors because of the nanowire linear dichroism of Sb_2Se_3; its movement can be controlled by adjusting the direction of incident light polarisation.[51] This technique may work well for targeted medication delivery, even if the authors did not conduct follow-up studies. Light energy has the ability to catalyse a redox reaction inside the micro/nanorobot in addition to directly propelling its movement. This process can further push the nanorobot by creating chemical gradients or bubbles.[52] It could provide exceptional movement and 3D motion control in a biological context and was non-toxic, extremely biocompatible, and ecologically benign. The inability of visible light to permeate tissues makes its application in biological systems difficult, notwithstanding the great findings of in vitro investigations. UV light-triggered photocatalytic TiO_2-Au Janus micromotor demonstrated strong driving capabilities.[53] However, exposure to UV rays will have negative effects, which will restrict its use. Since it may enter tissues with little adverse effects, near infrared (NIR) light has gained a lot of attention lately.[54] shown how to use NIR light to create a nanorobot system that could move in a certain direction. The Au half-nanoshell could provide a heat gradient and self-thermophoretic energy to overcome Brownian motion. Additionally, the membrane of a macrophage cell covered this system, giving the nanorobot immunological capabilities that allow it to actively identify and attach to cancer cells. Despite the potential of light energy powered by nanorobots, the majority of current research is done in vitro. It is worthwhile to thoroughly investigate if the directed movement of a complex interior environment may function as well as invitro. Furthermore, it is uncommon to find micro/nanorobots that are powered solely by light energy for drug delivery; instead, light energy usually combines with other energy sources to either accelerate the movements of the micro/nanorobots or initiate the release of pharmaceuticals at the intended location.[54]

3. Ultrasound Energy Propelled Micro/Nanorobots :

Active targeted drug administration is a promising application for ultrasonic-powered nanorobots because of their exceptional biocompatibility and dependability. Typically composed of gold, ultrasonic-driven nanorobots are commonly transported by nanowires. Ultrasound-propelled micro/nanomotors are designed using the template electrodeposition method extensively: First, the nanomotor's copper sacrificial layer was deposited in one end, creating a concave cavity. When ultrasonic waves entered the concave end, the pressure gradient that was established could propel the nanomotor forward.[55] Ultrasound is commonly combined with magnetic field. Victor et al. designed a magnetically guided three segment Au–Ni–Au nanowire motor which was propelled by ultrasound [56] Ultrasound propelled particles moved in both directions when the direction of the applied magnetic field changed. By including a polymeric (PPy-PSS) segment containing pH-sensitive medications inside the nanomotor, which could release the drug in an acidic environment, the ability of targeted drug delivery has been verified. Victor et al. created a four-segmented, ultrasound propelled nanorobot that used Au wire and Au–Ni–Au.[57] Ultrasound accelerated the nanoparticle's migration towards the cancer cells, whereas NIR light activation initiated the release of the loaded medication. Dox was loaded into this model, moved in the direction of the HeLa cell, and after 15 minutes of NIR irradiation, 38% of the drug was released. For intracellular siRNA delivery, a gold nanowire wrapped with a rolling circle amplification DNA strand that could hybridise with siRNA was created. [58] The pressure gradient created by ultrasound caused it to move in a certain way. After a few minutes of treatment, siRNA operated as scissors to divide the target mRNA with a 94% silencing efficiency. The nanorobot was able to enter the cell efficiently thanks to the rapid and enormous shove that ultrasound supplied. Ultrasound has sufficient penetration and can give nanorobots a powerful propulsion ability to get past the obstacles created in the intricate environment of the human body as compared to other energy-driven techniques. Nevertheless, using ultrasound could put cells under oxidative stress.[59] which might a ect normal cells besides the targeted cells.

Other applications of robots :

1. **Robots for sensing :**

Micro/nanorobots' unique properties of self-governing motion, simple surface functionalisation, and active target analyte detention and separation in complicated biological media have offered a great chance to achieve a number of difficult biosensing procedures pertaining to precise disease detection. The availability of artificial nanomotors, functionalised by multiple sample receptors, is necessary for the micro/nanorobot sensing technique to identify "on-the-fly" target biomolecular interactions. Strong binding and carrier capabilities of these receptor-bound/coated micro/nanomotors have led to the development of new techniques for identifying and separating biological targets in untreated bodily fluids, such as proteins, cancer cells, and nucleic acids. [60] Continuous attempts to functionalise synthetic motors have resulted in built-in solution mixing in microlitre clinical samples, which significantly improves the specific binding efficacy and provides the highest precisions in the sensitivity and speed of biological assays.[61] Furthermore, in addition to their unique motion control inside microchannel systems, these self-propelled nanomotors' efficient cargo towing capability could lead to the development of novel therapeutic and diagnostic microchips powered by active transport.[62]

2. **Robots for detoxification** :

Self-propelling micro/nanorobots are also used as a popular detoxifying technique because of their superior cleaning capabilities. Similar to biosensing, detoxification methods rely on self propelled micro/nanorobots that swiftly stop and remove the toxin to lessen the amount of non-toxic materials in the environment. Regarding the novel nanoscale biodetoxification system, the efficient movement would aid in the collision and toxins-motor binding covered with anticipated useful ingredients, such as nanomotors combined with natural ingredients derived from cells that are adept at mimicking the natural assets of their source cells. RBCs have proven to be exceptionally effective in acting as toxin-absorbing nanosponges to neutralise and remove dangerous "pore-forming toxins" (PFTs) from the bloodstream when compared to other cell products.[63] Many different forms of cell-mimicking micromotors have been developed for detoxification, activated by the biological characteristics of red blood cells. Wu et al., for instance, created a water-powered, cell-mimicking micromotor based on magnesium microparticles coated with RBC membranes that can effectively attract and neutralise toxins in biological fluids.[64] RBC membranes and ultrasound-propelled nanomotor combinations, such as a biomimetic stand, were found to effectively fascinate and neutralise PFTs by another detoxification method. A self-propelled three-dimensional (3D) printed microfish made of polydiacetylene nanoparticles, which aid in the absorption, confinement, and counteraction of toxins by binding contact, was used in another similar technique . Self-propelled 3D microfish raised in toxic solution showed advanced fluorescence strengths comparable to static microfish, highlighting the importance of active movement to improve detoxification outcomes.[65]

3. **Robots for precision surgery :**

Developments in robotic surgical systems have improved the skills of human surgeons and reduced issues associated with complex surgical procedures. This surgery using a robot is a quick growing field that enables physicians to perform a variety of somewhat aggressive actions with remarkable control, accuracy, and suppleness. Small robots, as opposed to their larger robotic counterparts, have the potential to move throughout the human body, operate in a variety of difficult-to-reach tissue locations, and address a wide range of medical issues.[66] The vast potential for resolving such constraints and challenges with these tiny devices for the most demanding surgical procedures has been opened by recent advancements in micro/nanorobots.[67] From nanodrillers to microgrippers and microbullets, these untethered micro/nanorobotic gadgets compromise unique capabilities for minimally invasive surgery. These micro/nanorobots have important advantages for extremely precise and minimally invasive surgery, but they also require proper management with a scope comparable to smaller biological units. Micro/nanorobots with nanoscale surgical mechanisms, powered by a variety of energy sources, can penetrate or re-enter cellular tissues for precise surgery. Unlike their larger robotic cousins, these tiny robots can go through the body's tiniest capillaries and carry out cellular-level operations. An important milestone towards the development of autonomous robotic devices for microsurgery is represented by tetherless microgrippers.Tissues and cells from difficult-to-reach locations may be stopped and reclaimed by such mobile microgrippers. The reduction and manoeuvrability of predictable microgrippers are restricted since they are typically attached and stimulated by mechanical or electrical waves generated from control systems via external connections (such as cables and tubes). The intriguing action of untethered microgrippers often involves the device opening and shutting, just like their great-bound counterparts.[68] In a recent study, Leong et al. have established a set of approachable microgrippers that may be triggered directly through various environmental features and employed as slightly invasive microsurgical devices[69] These microgrippers, which have morphologies demonstrated after biological attachments and articulated numbers arranged in various ways throughout a central palm, may be mass-produced using traditional multilayer photolithography. Soft microgrippers that rely on an integrated self-folding actuation reaction—

activated by their surrounding biological environment—eschew the need for external tethers. Various response mechanisms that are dependent on temperature, pH, or enzyme stimuli have been found to independently activate self-folding microgrippers in a given environment.[70]

Conclusions :

More coordinated research studies are needed to enhance the usefulness and dependability of small-scale robot systems, which are still quite novel and in their infancy. It has been demonstrated that a number of intelligent medical micro and nanorobots hold promise for precise cancer treatment and drug delivery to tumours. In this work, we examined recent advancements in medication delivery using micro- and nanorobots as well as other medicinal applications. Although micro/nanorobots can be used in deep tissue for real-time control and monitoring as well as to carry out complex tasks, there are a number of obstacles to overcome, such as communication, robot localisation and removal from the body, ease of preparation, improved drug delivery efficiency, unwanted immunological reactions, biocompatibility, biodegradability, and control challenges. Coordinated efforts should be made to standardise the procedures and metrics used to describe the actions of the devices, such as the management of illnesses, the targeted administration of therapeutic substances (drugs and cells), and diagnostic agents**.**

References :

1. Gupta D, Sharma M, Chaudhary V, et al. Robotic technolo gies in biomedical and healthcare engineering: microrobots and nanorobots in the refinement of modern healthcare practices. New York (NY): CRC Press Taylor&Francis group; 2021.

2. Kim Y, Lee J, Kang J, et al. A study on the development of medical robotics technology commercialization model. J Adv Inf Technol. 2021;12(2):148–152.

3. E stape R. Robotic surgery: single-site robotic surgery in gynecology. Berlin: Springer; 2021.

4. Agrahari V, Agrahari V, Chou ML, et al. Intelligent micro-/ nanorobots as drug and cell carrier devices for biomedical therapeutic advancement: promising development opportu nities and translational challenges. Biomaterials. 2020;260: 120163.

5. Sindhu RK, Kaur H, Kumar M, et al. The ameliorating approach of nanorobotics in the novel drug delivery sys tems: a mechanistic review. J Drug Target. 2021;29(8): 822–833.

6. H uang T-Y, Qiu F, Tung HW, et al. Cooperative manipula tion and transport of microobjects using multiple helical microcarriers. Rsc Adv. 2014;4(51):26771–26776.

7. Hu M, Ge X, Chen X, et al. Micro/nanorobot: a promising targeted drug delivery system. Pharmaceutics. 2020;12(7): 665.

8. Chen W, Sun M, Fan X, et al. Magnetic/pH-sensitive double layer microrobots for drug delivery and sustained release. Appl Mater Today. 2020;19:100583.

9. Nguyen HV, Faivre V. Targeted drug delivery therapies inspired by natural taxes. J Control Release. 2020;322: 439–456.

10. Dutta D, Sailapu SK. Intelligent nanomaterials for drug delivery applications: biomedical applications of nanobots. Amsterdam: Elsevier; 2020.

11. Li D, Liu C, Yang Y, et al. Micro-rocket robot with all-optic actuating and tracking in blood. Light Sci Appl. 2020;9:84.

12. Wu Z, Chen Y, Mukasa D, et al. Medical micro/nanorobots in complex media. Chem Soc Rev. 2020;49(22):8088–8112.

13. Soto F, Wang J, Ahmed R, et al. Medical micro/nanorobots in precision medicine. Adv Sci. 2020;7(21):2002203

14. Long X, Ye J, Zhao D, et al. Magnetogenetics: remote non invasive magnetic activation of neuronal activity with a magnetoreceptor. Sci Bull. 2015;60(24):2107 2119.

15. Ricotti L, Cafarelli A, Iacovacci V, et al. Advanced micro nano-bio systems for future targeted therapies. Curr Nanosci. 2015;11(2):144–160.

16. Luo M, Feng Y, Wang T, et al. Micro-/nanorobots at work in active drug delivery. Adv Funct Mater. 2018;28(25):1706100.

17. Sarath KS, Beena PN, Elessy A. Nanorobots a future device for diagnosis and treatment. J Pharm Pharmaceut. 2018; 5(1):44–49.

18. Ghoshal IK, Mahanti S, Goswami S, et al. Importance of nanorobotics in pharma and medical field. World J Pharm. Res. 2020;9(8):726–738.

19. S oto F, Chrostowski R. Frontiers of medical micro/nanoro botics: in vivo applications and commercialization perspec tives toward clinical uses. Front Bioeng Biotechnol. 2018;6: 170.

20. Singh AV, Ansari MH, Laux P, et al. Micro-nanorobots: important considerations when developing novel drug delivery platforms. Expert Opin Drug Deliv. 2019;16(11): 1259–1275.

21. Sachdeva S, Mani A, Mani SA, et al. Nano-robotics: the future of health and dental care. IP Int J Periodontol Implantol. 2021;6(1):6–10.

22. Znidarsic A, Baggia A, Werber B. Attitudes toward micro chip implant in groups pro and con its insertion for health care purposes. 2020. BLED 2020 Proceedings 1; [cited 2021 Oct 28]. Available from: https://aisel.aisnet.org/bled2020/1.

23. Kumar JP, Sankaranarayanan R, Sujana JA, et al. Nanomedicine manufacturing and applications: advantages and disadvantages of nanodevices. Amsterdam: Elsevier; 2021.

24. Manjunath A, Kishore V. The promising future in medicine: nanorobots. Biomed Sci Eng. 2014;2(2):42–47.

25. Gandhi M, Joshi PN. Nanobiomaterial engineering: nanoro bots for in vivo monitoring: the future of nano-implantable devices. Singapore: Springer; 2020.

26. Javaid A. Medical nanorobots: our new healthcare defense. Academia Letters. 2021;2021:1629..

27. Sapra V, Sapra L, Sandhu JK, et al. Nanotechnology: bio medical diagnostics through nanocomputing. New York (NY): Jenny Stanford Publishing; 2021.

28. Xu K, Xu S, Wei F. Recent progress in magnetic applications for micro-and nanorobots. Beilstein J Nanotechnol. 2021; 12(1):744–755.

29. Mertz L. Tiny conveyance: Micro- and nanorobots prepare to advance medicine. IEEE Pulse. 2018;9(1):19–23.

30. Howes OD, Rogdaki M, Findon JL, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British association for psycho pharmacology. J Psychopharmacol. 2018;32(1):3–29.

31. Conti D, Trubia G, Buono S, et al. Evaluation of a robot assisted therapy for children with autism and intellectual disability. Annual conference towards autonomous robotic systems. Singapore: Springer; 2018..

32. Libin AV, Libin EV. Person-robot interactions from the robopsychologists point of view: the robotic psychology and robotherapy approach. Proc IEEE. 2004;92(11): 1789–1803.

33. Riek LD. Healthcare robotics. Commun Acm. 2017;60(11): 68–78.

34. Medina-Sanchez M, Xu H, Schmidt OG. Micro- and nano motors: the new generation of drug carriers. Ther Deliv. 2018;9(4):303–316.

35. Tang S, Zhang F, Gong H, et al. Enzyme-powered janus platelet cell robots for active and targeted drug delivery. Sci Robot. 2020;5(43):eaba6137.

36. Shao J, Xuan M, Zhang H, et al. Chemotaxis-guided hybrid neutrophil micromotors for targeted drug transport. Angew Chem. 2017;129(42):13115–13119.

37. Felfoul O, Mohammadi M, Taherkhani S, et al. Magneto aerotactic bacteria deliver drug-containing nanoliposomes to tumour hypoxic regions. Nat Nanotechnol. 2016;11(11): 941–947.

38. Wu Z, Lin X, Zou X, et al. Biodegradable protein-based rockets for drug transportation and light-triggered release. ACS Appl Mater Interfaces. 2015;7(1):250 255.

39. Ma X, Hahn K, Sanchez S. Catalytic mesoporous janus nano motors for active cargo delivery. J Am Chem Soc. 2015; 137(15):4976–4979.

40. Mou F, Chen C, Zhong Q, et al. Autonomous motion and temperature-controlled drug delivery of Mg/Pt-poly (N-iso propylacrylamide) janus micromotors driven by simulated body fluid and blood plasma. ACS Appl Mater Interfaces. 2014;6(12):9897–9903.

41. Gao W, Kagan D, Pak OS, et al. Cargo-towing fuel-free mag netic nanoswimmers for targeted drug delivery. Small. 2012;8(3):460–467.

42. Walker D, K€ asdorf BT, Jeong H-H, et al. Enzymatically active biomimetic micropropellers for the penetration of mucin gels. Sci Adv. 2015;1(11):e1500501.

43. Ma X, Sanchez S. Self-propelling micro-nanorobots: chal lenges and future perspectives in nanomedicine. Nanomedicine. 2017;12(12):1363–1367.

44. Kagan D, Laocharoensuk R, Zimmerman M, et al. Rapid delivery of drug carriers propelled and navigated by cata lytic nanoshuttles. Small. 2010;6(23):2741–2747.

45. Wu Z, Wu Y, He W, et al. Self-propelled polymer-based multilayer nanorockets for transportation and drug release. Angew Chem Int Ed Engl. 2013;52(27):7000–7003.

46. Schmidt CK, Medina-Sanchez M, Edmondson RJ, et al. Engineering microrobots for targeted cancer therapies from a medical perspective. Nat. Commun. 2020;11(1):1–8.

47. Chen X-Z, Hoop M, Mushtaq F, et al. Recent developments in magnetically driven micro-and nanorobots. Appl Mater Today. 2017;9:37–48.

48. Demirörs, A.F.; Akan, M.T.; Poloni, E.; Studart, A.R. Active cargo transport with Janus colloidal shuttles using electric and magnetic fields. Soft Matter 2018, 14, 4741–4749. [CrossRef] [PubMed]

49. Rahman, M.; Chowdhury, M.M.; Alam, K. Rotating-Electric-Field-Induced Carbon Nanotube-Based Nanomotor in Water: A Molecular Dynamics Study. Small 2017, 13, 1603978. [CrossRef] [PubMed]

50. Liang, Z.; Teal, D.; Fan, D.E. Light programmable micro/nanomotors with optically tunable in-phase electric polarization. Nat. Commun. 2019, 10, 5275. [CrossRef] [PubMed]

51. Zhan, X.; Zheng, J.; Zhao, Y.; Zhu, B.; Cheng, R.; Wang, J.; Liu, J.; Tang, J.; Tang, J. From Strong Dichroic Nanomotor to Polarotactic Microswimmer. Adv. Mater. 2019, 31, e1903329. [CrossRef]

52. Kong, L.; Mayorga-Martinez, C.C.; Guan, J.; Pumera, M. Photocatalytic Micromotors Activated by UV to Visible Light for Environmental Remediation, Micropumps, Reversible Assembly, Transportation, and Biomimicry. Small 2019, e1903179. [CrossRef]

53. Dong, R.; Hu, Y.; Wu, Y.; Gao, W.; Ren, B.; Wang, Q.; Cai, Y.-P. Visible-Light Driven BiOI-Based Janus Micromotor in Pure Water. J. Am. Chem. Soc. 2017, 139, 1722–1725. [CrossRef]

54. Wang, Q.; Dong, R.-F.; Wang, C.; Xu, S.; Chen, D.; Liang, Y.; Ren, B.; Gao, W.; Cai, Y.-P. Glucose-Fueled Micromotors with Highly E cient Visible-Light Photocatalytic Propulsion. ACS Appl. Mater. Interfaces 2019, 11, 6201–6207. [CrossRef]

55. Dong,R.; Zhang, Q.; Gao, W.; Pei, A.; Ren, B. Highly E cient Light-Driven TiO_2–Au Janus Micromotors. ACSNano2016, 10, 839–844. [CrossRef]

56. Villa, K.; Pumera, M. Fuel-free light-driven micro/nanomachines: Artificial active matter mimicking nature. Chem. Soc. Rev. 2019, 48, 4966–4978. [CrossRef] [PubMed]

57. Wu,Z.;Si, T.; Gao, W.; Lin, X.; Wang, J.; He, Q. Superfast Near-Infrared Light Driven Polymer Multilayer Rockets. Small 2015, 12, 577–582. [CrossRef] [PubMed]

58. Xuan,M.; Shao, J.; Gao, C.; Wang, W.; Dai, L.; He, Q. Self-Propelled Nanomotors for Thermomechanically Percolating Cell Membranes. Angew. Chem. Int. Ed. 2018, 57, 12463–12467. [CrossRef] [PubMed]

59. Li, J.; Li, T.; Xu, T.; Kiristi, M.; Liu, W.; Wu, Z.; Wang, J. Magneto–Acoustic Hybrid Nanomotor. Nano Lett. 2015, 15, 4814–4821. [CrossRef] [PubMed]

60. Park S, Yossifon G. Micromotor-based biosensing using directed transport of functionalized beads. ACS Sens. 2020; 5(4):936–942

61. Wang J. Self-propelled affinity biosensors: moving the receptor around the sample. Biosens Bioelectron. 2016;76: 234–242.

62. Molinero-Fernandez A, Arruza L, Lopez MA, et al. On-the-fly rapid immunoassay for neonatal sepsis diagnosis: C-reactive protein accurate determination using magnetic graphene based micromotors. Biosens. Bioelectron. 2020;158:112156.

63. Hu C-MJ, Fang RH, Copp J, et al. A biomimetic nanosponge that absorbs pore forming toxins. Nat Nanotechnol. 2013; 8(5):336–340.

64. Wu Z, Li J, de Avila BE, et al. Water-powered cell-mimicking janus micromotor. Adv Funct Mater. 2015;25(48):7497–7501

65. Zhu W, Li J, Leong YJ, et al. 3D-printed artificial microfish. Adv Mater. 2015;27(30):4411–4417.

66. Yang Y, Bevan MA, Li B. Efficient navigation of colloidal robots in an unknown environment via deep reinforcement learning. Adv Intell Syst. 2020;2(1):1900106.

67. Zhong Y, Hu L, Xu Y. Recent advances in design and actu ation of continuum robots for medical applications. Actuators. 2020;9(4):142.

68. Zhang J, Salehizadeh M, Diller E. Parallel pick and place using two independent untethered mobile magnetic micro grippers. 2018 IEEE International conference on robotics and automation (ICRA); 2018. p. 123–128.

69. Leong TG, Randall CL, Benson BR, et al. Tetherless thermo biochemically actuated microgrippers. Proc Natl Acad Sci USA. 2009;106(3):703–708.

70. Jia H, Mailand E, Zhou J, et al. Universal soft robotic micro gripper. Small. 2019;15(4):1803870.