Chapter

Smart Drug Delivery for Targeted Therapeutics via Remotely Controlled Microdevices

Negar Fouladvari, Roberto Bernasconi and Luca Magagnin

Abstract

Remotely controlled smart drug delivery systems represent a remarkable integration of materials science, physics, and biology. They offer precise control over drug delivery through tailored adjustments in shape, size, and material composition. Microdevices for targeted delivery can be manufactured using a wealth of techniques, like 3D printing or lithography, enabling accurate control at the microscale. Smart materials sensitive to external stimuli like temperature, pH and electric or magnetic field variations can be exploited to enable targeted drug delivery. This interdisciplinary approach aims at refining drug administration precision, minimizing side effects and maximizing therapeutic impact. The impact of these technologies is potentially groundbreaking, envisioning a future where medical treatments are not only more effective but also finely tuned to individual patient needs. This chapter aims to discuss the current literature on drug delivery microrobots, emphasizing the strategies employable to integrate smart delivery functionalities on remotely actuated microcarriers.

Keywords: targeted drug delivery, microrobots, microdevices, remote control, healthcare innovation

1. Introduction

Drug delivery systems (DDSs) transport therapeutic drugs to achieve desired effects on well-defined target organs inside the human body [1]. They aim at enhancing drug solubility, stability, and pharmacological activity while minimizing side effects [2]. One of the most interesting examples of advanced DDSs is the so-called biomedical microrobots. Indeed, miniaturized untethered medical robots, driven by advancements in microtechnology, promise to revolutionize minimally invasive therapeutic procedures. These tiny devices, equipped with micro-actuators and in some cases sensors, are able to navigate intricate paths within the body and carry out complex tasks. Utilizing precise movements and real-time data feedback, they enhance accessibility and reduce invasiveness for what concerns drug delivery duties. Their potential to improve patient outcomes marks a significant advancement in medical technology [3].

Microdevices will potentially play a crucial role in modern DDSs by offering precise, controlled, and targeted delivery of therapeutic agents [4]. In general, they encompass specific tools, which allow them to work with minimal solution volumes in order to enable a wide range of tasks, including target immobilization, detection, laboratory testing, transport, etc. [5]. In the specific case, these miniature devices can be engineered to release drugs at specific rates, locations and times, enhancing the efficacy and reducing the side effects of treatments. For example, implantable microdevices can deliver medication directly to a target area, such as a tumor, minimizing systemic exposure and side effects [4]. Untethered microdevices can also borrow some of the functionalities typical of microfluidic devices, facilitating diagnostic and monitoring functions by detecting biomarkers within various body fluids or analyte-containing solutions [6]. Progress in fabrication strategies and miniaturization technologies has facilitated the development of biomedical microdevices aimed at assisting in the diagnosis, monitoring, and treatment of a range of chronic and non-chronic illnesses [7].

Microdevices can also be integrated with smart technologies, allowing for real-time monitoring and adjustment of drug delivery based on the patient's needs. This approach not only improves the precision of treatment but also enables personalized medicine, where the therapy is tailored to the individual patient's condition and response [8]. From this point of view, the effectiveness of biomedical microrobots can be further improved by implementing them with materials able to release drugs only in correspondence with specific external stimulation. Indeed, stimuli-responsive delivery stands out as a leading strategy in drug delivery, aiming for specific disease delivery and controlled release. Endogenous triggers such as diffusion, ROS (reactive oxygen species), pH, enzymes or temperature may potentially target release on specific disease sites like tumors. Exogenous stimuli like light or temperature can also trigger responses, and magnetic or electric fields are utilized as well. In addition, even ultrasounds offer the possibility to carry out remote control by delivering localized heat for precise release within the body, enhancing site-specific control [9]. DDSs employing microdevices may utilize several mechanisms to achieve targeted and controlled release of drugs, but their functioning at the microscale experiences completely different physical interactions with the surrounding environment compared to their macro counterparts [10]. This aspect must be carefully considered during their design.

In this chapter, some key mechanisms for drug loading and release that can be implemented in microrobotic devices are discussed. These include, for example, advanced drug loading technologies or the use of responsive materials that react to external stimuli (for example, pH, light, or heat) to trigger the drug release. In addition, remote control mechanisms such as wireless control or magnetic actuation are discussed [11]. The primary objective of the chapter is to provide a comprehensive review on drug-releasing microdevices and to investigate the various release mechanisms they employ for accurate and controlled drug delivery. By exploring the complex world of microrobots, this chapter aims to clarify the interaction between miniature devices and the precise release of therapeutic agents. Through explanations and examples, readers will gain a general understanding of how microdevices work and of the mechanisms they utilize to achieve controlled drug release. Readers will be equipped with the knowledge necessary to appreciate the complexity and potential of untethered microdevices in the realm of targeted drug delivery, opening the path for advancements in precision medicine and improved patient outcomes.

2. Microrobots

2.1 Base concepts

"Micro robotics is not simply about making traditional robots smaller" [10].

Microdevices can enhance drug therapy by enabling precise and complex dosing, reducing pain, and improving patient compliance. Historically, microneedles have been tested on humans and other drug-delivery devices have demonstrated promise in both in vitro and in vivo studies [12]. In the late twentieth century, the introduction of microrobotics revolutionized our scientific outlook, offering vast potential across diverse fields. From micromanipulation, environmental remediation and precision sampling to drug delivery, point-of-care clinical diagnostics and sensitive bioanalytical systems, their applications span the spectrum of scientific and biomedical domains, reshaping our understanding and capabilities [13]. In the case of the topic treated in the present chapter, transitioning to microrobotics demands a shift in engineering intuition and the cultivation of novel perspectives. Microrobotics extends beyond conventional robotics, requiring expertise in physics, material science, and biology [10]. Furthermore, as the possibility of utilizing microdevices in mass production increases, there is a critical need to advance analytical models to determine flow and transport phenomena, optimize design and control methodologies, and enhance sensing and monitoring performances [14].

The concept of "medical microrobots" is to non-invasively in-vivo navigate the body and enhance healthcare outcomes. This can be done by providing real-time diagnosis, monitoring diseases like Alzheimer's, measuring glucose levels in individuals with diabetes, sending robotic swarms to deliver precise therapies to tumors or performing minimally invasive surgery perhaps in the eye or even in the brain [15]. In general, microrobots offer the promise of reaching inaccessible body regions through natural pathways. Their wireless connectivity can potentially mitigate many limitations associated with systemic treatments and facilitate innovative minimally invasive procedures [16].

As already mentioned, microrobots experience different physical interactions with respect to macroscopic machines. Certainly, the laws of physics remain constant at the microscale, but their relative influence on the behavior of microfluidic devices can vary significantly due to the unique characteristics of microscale phenomena. At the microscale, various physical principles such as surface tension, viscosity, and capillary forces become more pronounced and dominant compared to macroscale systems. Micromachines typically operate within the low Reynolds number (Re) regime, which is characterized by the dominance of viscous forces over inertial forces. The Reynolds number (Re) is a dimensionless quantity used to predict fluid flow patterns and transitions between different flow regimes. It is defined by Eq. (1).

$$\mathrm{Re} = \frac{\rho.v.L}{\mu} \tag{1}$$

Where ρ is the fluid density, v is the characteristic velocity of the flow (in this case, of the microdevice), L is the characteristic length scale (such as the largest dimension of the microdevice), and μ is the dynamic viscosity of the fluid. Re represents the ratio between inertial (F_i) and viscous (F_v) forces acting on the system (Eq. (2)).

$$\mathrm{Re} = \frac{F_i}{F_v} \tag{2}$$

Purcell's work on low Reynolds number flows in 1977 is fundamental to understand the behavior of fluids at small scales, where viscous forces dominate over inertial forces. At low Reynolds numbers ($Re \ll 1$), which typically occur in microfluidic systems and biological environments, fluid dynamics are primarily governed by viscosity rather than inertia. Volume-related forces tend to become negligible with respect to surface-related forces. Under these conditions, the fluid dynamics of the system is characterized by instantaneous and time-reversible flows. Indeed, these highly reversible flows around objects swimming at the microscale make reciprocal motion impossible and the dynamics are dominated by viscosity rather than inertia. The "Scallop Theorem" in physics states that in a highly viscous fluid environment characterized by low Reynolds numbers, a swimmer or an object undergoing reciprocal motion cannot achieve net displacement. This means that if a swimmer moves back and forth in a symmetrical manner, the fluid forces generated will cancel each other out over a complete cycle, resulting in no overall movement [17].

Consequently, microrobots can only be actuated with non-reciprocating actuation strategies and this basically translates into four possibilities. The most obvious is

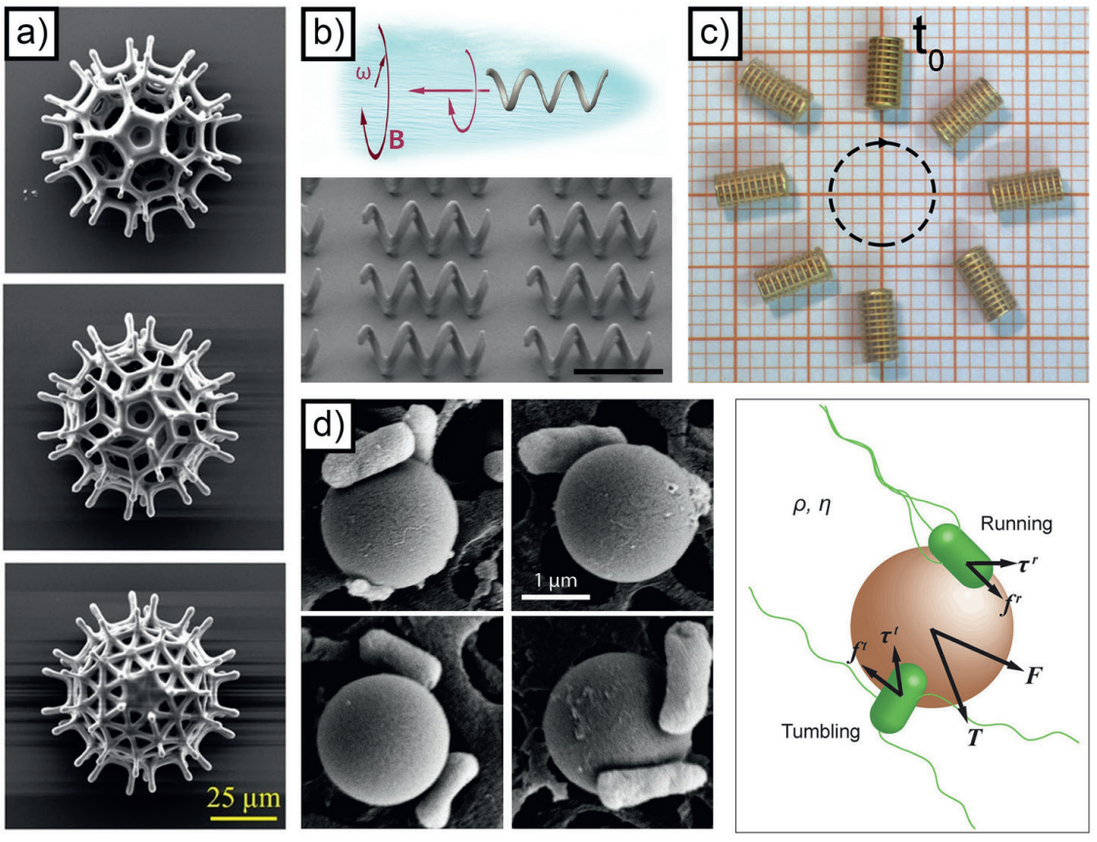

Figure 1.
Complex shaped microrobots propelled by the direct application of a magnetic force (a); base concept behind helical microdevices propelled by a rotating magnetic field and SEM image of a 3D printed array on a glass substrate (b, scale bar 10 µm); circular pattern actuation of a microdevice in contact with a glass surface (c); base concept and SEM images of bacteria-driven micro swimmers with a spherical body (d). Reprinted with permission from [18–21].

direct propulsion, where the device is directly pulled or pushed by a force (**Figure 1a**) [18]. The second possibility is the swimming motion, which is inspired by the cilia and flagella used by many procaryotic cells. In this case, the device swims into the fluid with a corkscrewing motion (**Figure 1b**) [19]. Non-reciprocating movements can be obtained also by exploiting the presence of solid surfaces or external bodies. For example, microrobots can be placed in contact with a solid surface and use friction to convert a rotative movement into a linear one (**Figure 1c**) [20]. Finally, a smart way to propel devices at the microscale is represented by the use of naturally occurring "micromotors", like prokaryotic cells. These can be connected to the microdevices and propel them using natural cilia and flagella (**Figure 1d**) [21].

2.2 Microrobots actuation

Keeping in mind the challenges connected to their reduced dimensions and the necessity of non-reciprocating motions, scientists have developed different methods to propel and guide microrobots toward their targets that can be inscribed into the four categories previously discussed [22]. For microrobot actuation, traditional motors cannot be used as power sources due to their size mismatch with the devices. Consequently, researchers have developed various alternative actuation methods, including the use of magnetic fields, electromagnetic fields, light, acoustic actuation or chemical propulsion [23]. Thanks to these tailored actuation approaches, untethered devices hold promise for revolutionary applications in medicine, biotechnology, environmental remediation, and beyond [22, 24]. Actuation mechanisms in microdevices are crucial for the manipulation and control of microscale components in a variety of applications such as biomedical purpose microrobots. These mechanisms convert various forms of energy into mechanical motion at the microscale. It is possible to use only one mechanism at a time or a combination of more than one mechanism, such as a temperature and electric field dual-stimulus.

The first form of propulsion historically adopted for microdevices propulsion is the chemical one. Chemically actuated microrobots exploit chemical reactions to induce and control their movements or functionalities at the microscale (**Figure 2a**) [25]. Microactuators driven by chemical reactions typically comprise two regions: one able to catalyze a chemical reaction or to work as an anode, the second inert or able to work as a cathode. The most typical example is the decomposition of hydrogen peroxide into water and oxygen. A device that uses this chemical fuel for its propulsion is composed of a bimetallic structure, which translates into an anodic and a cathodic region. The resulting self-electrophoresis effect (the spontaneous generation of a chemical gradient around the device able to move it) propels the device. Chemically propelled devices can also rely on the direct chemical degradation of a suitable species or on self-diffusiophoresis [29]. Beside the two regions present on the surface, the device can be composed of additional layers, which act as a supportive substrate that facilitates actuation [30].

The most common and promising (from the applicative point of view) actuation route is, however, magnetic actuation (**Figure 2b**) [26]. In this method, a magnetic field is applied to a device that is composed for a certain fraction of its mass of ferromagnetic or superparamagnetic material. Such magnetic material responds to the application of an external field with a force F_m or a torque T_m, which are expressed by Eqs. (3) and (4), respectively.

$$\overrightarrow{F_m} = \int_V \left(\vec{M} \cdot \nabla\right) \vec{B} dV \tag{3}$$

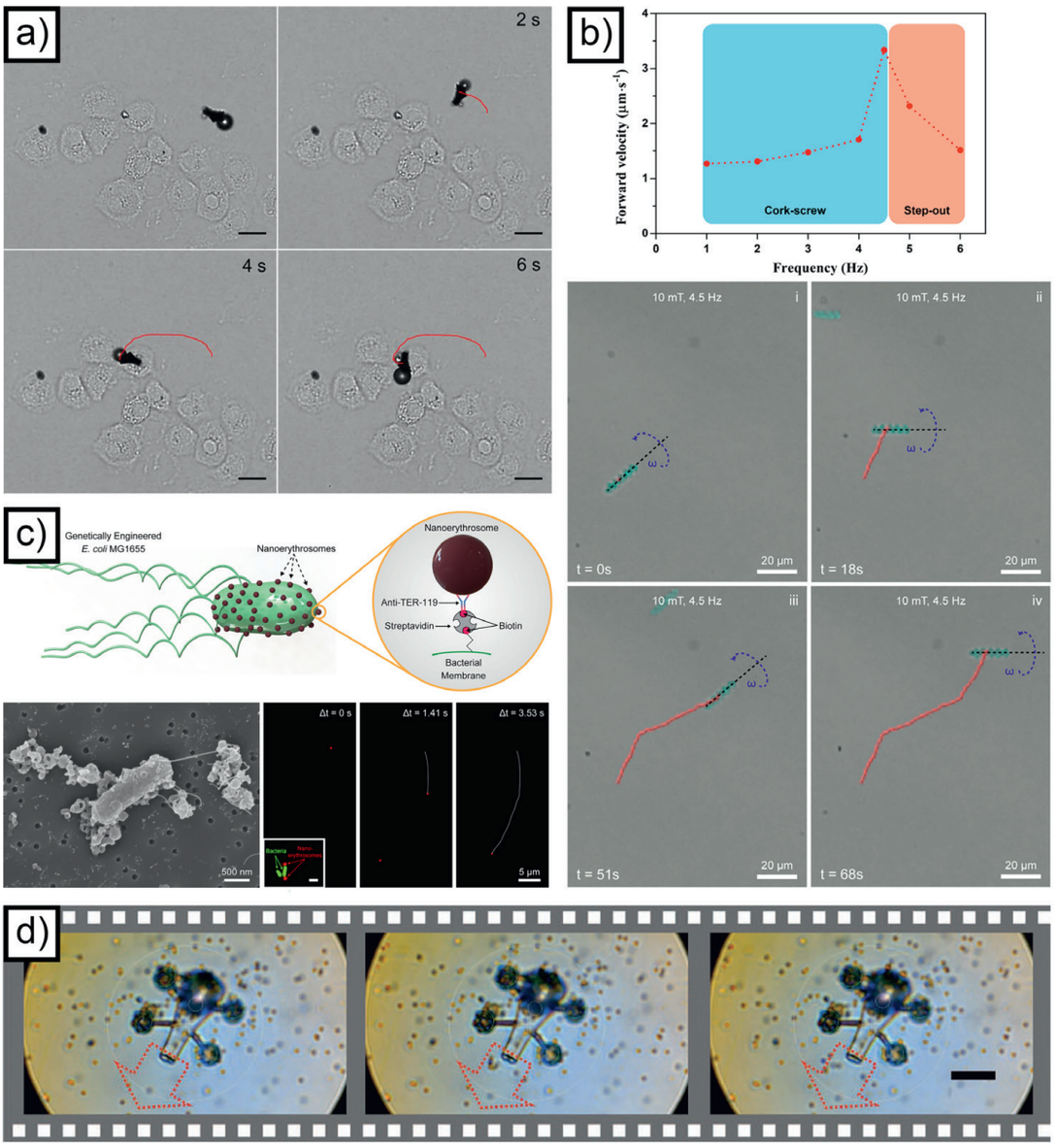

Figure 2.
Time-lapse images of the movement of hydrogen peroxide chemically propelled microrockets toward sheets of Hela cells (a; scale bar = 20 μm); actuation and steering of ABFs microswimmers using a rotating magnetic field (b); base concept and SEM images of biohybrid bacterial microswimmers functionalized with red blood cells (c); light-driven micro-tool equipped with a syringe function (d). Reprinted with permission from [25–28].

$$\overrightarrow{T_m} = \int_V \vec{M} \times \vec{B} dV \tag{4}$$

Where V is the volume of magnetic material, B is the external magnetic field and M is the magnetization. As a consequence, the device can be moved in a very precise way by applying gradients, oscillating or rotating magnetic fields. In addition to the great precision achievable during actuation, magnetic field is not harmful to the human body and it represents the most interesting strategy to actuate drug-releasing devices that must operate in-vivo.

Typically, in order to get non-reciprocating motion, magnetic microrobots are controlled within a workspace using two primary methods: utilizing a rotating

magnetic field for swimming motion, or directly propelling them with a magnetic gradient. In the case of rotational motion, a magnetic torque spins an asymmetric structure like a helix to generate forward thrust (**Figure 1b** and **2b**). Such structures, due to their similarity with naturally occurring prokaryotic flagella, are named artificial bacteria flagella (ABF). For translational movement, a magnetic gradient directly applies a propulsive force on microrobots (**Figure 1a**), enabling precise control over their desired translational degrees of freedom (DOF) [31, 32]. A special type of magnetic actuation is the so-called rolling motion, which exploits the contact with a solid surface and can be assimilated to a wheel that rotates under the influence of a magnetic torque (**Figure 1c**). The linear speed is proportional to the radius of the microdevice and to the rotation frequency [33]. The actuability of this kind of device was demonstrated by applying rotating magnetic fields on devices containing a semi-hard magnetic material like CoNiP [34]. Finally, also more complex magnetic actuation strategies based on the use of oscillating fields and complex magnetic patterns have been implemented [35].

Magnetic actuation generally requires the generation of highly controlled fields and gradients. This can be achieved, for example, by means of the so-called electromagnetic field actuation (EMA), which involves the use of electromagnets to induce and control the motion at the microscale. This method relies on the interaction between an external magnetic field generated by current-carrying coils and the magnetic materials present in the devices to achieve movement and manipulation. To control untethered microrobots effectively, the electromagnetic actuation (EMA) system must be carefully designed to ensure adequate propulsion aligned with specific application goals. It is crucial to develop an EMA setup that is efficient, provides sufficient degrees of freedom (DOF), and avoids singularities [36].

Optically actuated microrobots use electromagnetic radiation to induce mechanical motion, either through photothermal effects or through optoelectronic mechanisms [24]. Such actuators are based, for example, on polymers modified with chromophores that can be employed for photomechanical actuation. Suitably designed optical actuators can be therefore integrated into microdevices, allowing reproducible and controlled actuation [37].

Another interesting approach to move devices at the microscale is the use of acoustic waves. Combining acoustic actuation with microrobots significantly broadens their application areas, thanks to its flexibility, biocompatibility, and controllability. Acoustically actuated microrobots can be classified into three common types based on their working principle: bubble propulsion, sharp-edge propulsion, and in-situ microrotors. Despite many examples available in literature, this category of microrobots is still in its early development stage and many challenges lie ahead [38].

Finally, microrobots can be propelled also by employing temperature gradients (**Figure 2d**) [39] or by integrating them with biological entities like bacteria or protozoans, resulting into the so-called bio-hybrid propulsion (**Figure 2c**) [27].

2.3 Microrobots production

Besides actuation, also the fabrication of micrometric-sized entities like microrobots is non-trivial. By employing a wide variety of materials (metals, polymers or ceramics), researchers fabricated remotely actuated devices using 3D printing, photolithography [40], bio-templating [41], sputtering deposition [42], wet deposition [43] or combinations of these techniques [44]. **Figure 3** schematizes the working principles of the most common fabrication techniques applicable to the manufacturing of microrobots.

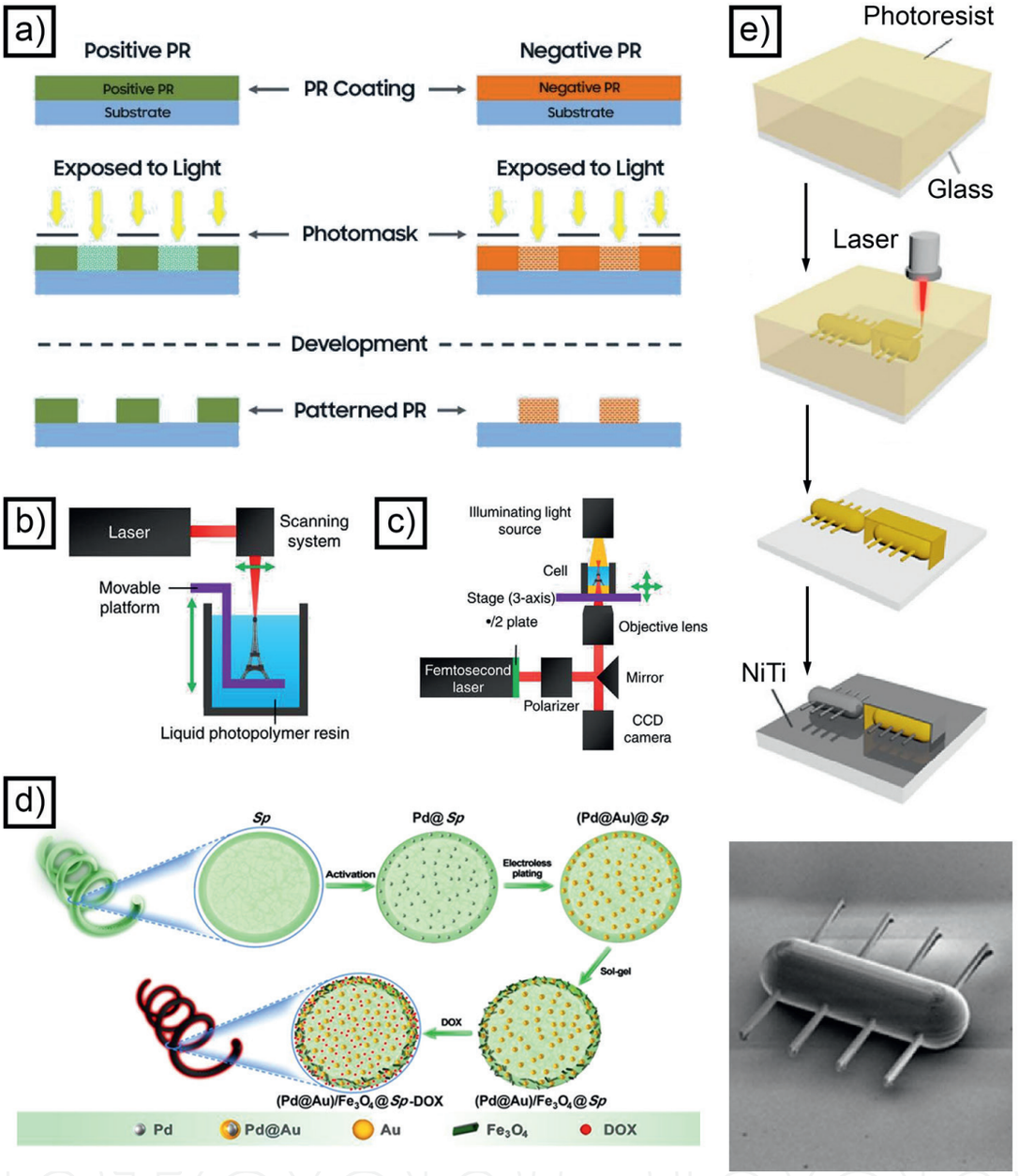

Figure 3.
Schematic representation of the lithography process (a); schematic representation of a stereolithography setup (b); schematic representation of a direct laser writing setup (c); manufacturing procedure for ABFs obtained by adsorbing magnetite nanoparticles on the surface of the cyanobacterium Arthrospira Platensis (d); microwalkers production by sputtering metal on DLW templates (e). Reprinted with permission from [45–47].

Most of the technologies employed to transfer patterns during microrobots fabrication are based on light. Photolithography stands out as a primary method for transferring intricate patterns onto substrates, forming the foundation of many fabrication processes (**Figure 3a**). The photolithographic process begins with the application of a photosensitive coating, often called photoresist (PR), onto the surface of the substrate. This coating is sensitive to light and undergoes a chemical change upon exposure. A mask, containing a precise image of the desired pattern, is then placed over the coated substrate. When exposed to light, the pattern on the mask is transferred onto the photoresist-coated substrate [48].

Also 3D printing stands as a powerful manufacturing technique [49], facilitating the production of biomedical devices and systems whose production would pose challenges with conventional methods like machining or molding. A variety of 3D printing technologies are available, prominently light-based approaches due to their superior resolution. Indeed, each modality presents distinct advantages and limitations [50], but light-based approaches like stereolithography (SLA, **Figure 3b**) and direct laser writing (DLW, **Figure 3c**) are the most used for the fabrication of micrometric structures like microrobots. SLA works by solidifying a photocurable liquid resin in 2D patterns by means of a laser. The resist absorbs single photons and the resulting 2D patterns constitute the single layers of the final object, which is therefore fabricated in a layer-by-layer fashion. DLW, and multi-photon polymerization (MPP), work in a similar way, but in this case the material absorbs more than one photon of light (allowing resolutions down to 100 nm). Moreover, DLW does not necessarily work in layer-by-layer way, allowing a higher flexibility in terms of printable shapes.

Besides pattern transferring, microrobots production strongly relies on a variety of post-processing techniques like sputtering or wet deposition. These are fundamental, for example, to deposit the metallic layers used in some magnetic devices fabricated via polymer-based 3D printing. For example, sputtering deposition can be used to deposit metallic layers on templates obtained by DLW (**Figure 3e**). Nanoparticle deposition or self-assembly approaches, finally, are fundamental for the vast majority of bio-templating fabrication routes. As a representative example, it is worth mentioning the deposition of magnetite nanoparticles on the Spirulina cyanobacterium (*Arthrospira platensis*). This micrometric living being is naturally characterized by a spiral structure and, by depositing some magnetic material on its surface, it is possible to obtain fully working ABFs (**Figure 3d**).

The production of microrobots is an intrinsically multidisciplinary field and it is not possible to enumerate all the different approaches described in the literature in a concise way. The cases reported are the most common and straightforward. In addition to these, a wealth of smart strategies have been proposed, like self-folding [51], inkjet assisted electroforming [52] or microfluidic gelation [53].

3. Drug loading on microdevices

Efficiently loading drugs on microrobots is a crucial part of their development and the strategy selected strongly depends on the working environment of the device and on its delivery profile. In general, the oral route for drug administration is highly preferred due to its convenience, affordability, and high patient compliance. However, despite these advantages, many small-molecule drugs and biotherapeutics face challenges when administered orally due to various physiological barriers, and as a result, drugs suffer from issues like low solubility, low permeability, and degradation following oral administration [54]. These limitations basically apply also to microrobots that navigate the human body through the digestive apparatus. Devices that travel into blood vessels, on the contrary, experience slightly different challenges connected to the presence of immune cells in the bloodstream and to the clearance action operated by the liver and the kidneys. Finally, all the types of drug-releasing devices potentially suffer from the same issue: off-target administration. This happens when a certain fraction of the drug released reaches non-target organs, potentially resulting in side effects and medical complications.

To overcome these challenges, pharmaceutical scientists employ various strategies to enhance the delivery of drugs. These include formulation approaches such as nanotechnology-based delivery systems, lipid-based formulations, prodrugs, mesoporous silica nanoparticles, and pH-sensitive coatings to protect drugs from degradation and enhance their absorption [55, 56]. In addition, many newly developed biotherapeutics, encompassing peptides, proteins, DNA, RNA, and other macromolecules, often exhibit optimal oral bioavailability [57]. Indeed, the development of permeation enhancers and transporter-targeted delivery systems can improve drug uptake across the intestinal epithelium [56].

The discovery of nanotechnologies, including nanoparticles, nanofibers, nanogels, micelles, and microspheres, has led to the development of innovative DDSs, which have become a promising tool in the pharmaceutical field [58]. There are several parameters to consider when designing microdevices, including drug-loading capacity, particle size and size distribution, biocompatibility, and thermodynamic and kinetic stability. Methods for drug loading on biomedical microdevices include a range of techniques tailored to suit specific device designs and drug types. Some common methods are discussed in the following sections with the support of some relevant examples.

3.1 Physical entrapment

Physical entrapment is widely used in DDSs to improve the stability, bioavailability, and controlled release of therapeutic agents. Drugs are physically entrapped within a continuous matrix or a porous structure without forming covalent bonds between the drug and the carrier. The positive points are that this method is simple and preserves drug activity. Another advantage is that it allows a controlled release through diffusion or matrix degradation. For example, the anticancer drug Adriamycin (ADR) can be incorporated into polymeric micelles formed from a poly(ethylene glycol)-poly(aspartic acid) block copolymer through physical entrapment [59]. Regarding the field of microrobotics, a notable example can be seen in the works shown in **Figure 4a** and **b**. In both papers [60, 61], the authors loaded rhodamine B (RhB) into various types of alginate hydrogels, which were applied on the surface of magnetically actuated microdevices. RhB did not interact significantly with the hydrogel chains and it was physically entrapped into the mesh of the swollen polymeric network.

3.2 Chemical conjugation

Chemical conjugation is a sophisticated method used to attach drugs to microdevices through the formation of stable covalent bonds. This technique enhances the stability and control over drug release, making it particularly useful for applications requiring precise drug delivery with a strong and stable attachment. This approach reduces the risk of drug strain and it is suitable for applications requiring long-term stability [63]. Moreover, the chemical bonds present between the matrix and the drug can be selectively broken by external stimuli, allowing smart drug release. Obviously, tuning the strength and type of bond formed between the drug and the matrix is fundamental to tune it release and avoid drug degradation. Applications can be found in biosensors, implantable devices and systems requiring prolonged drug retention [64]. For what concerns microrobots, a few examples of chemically conjugated

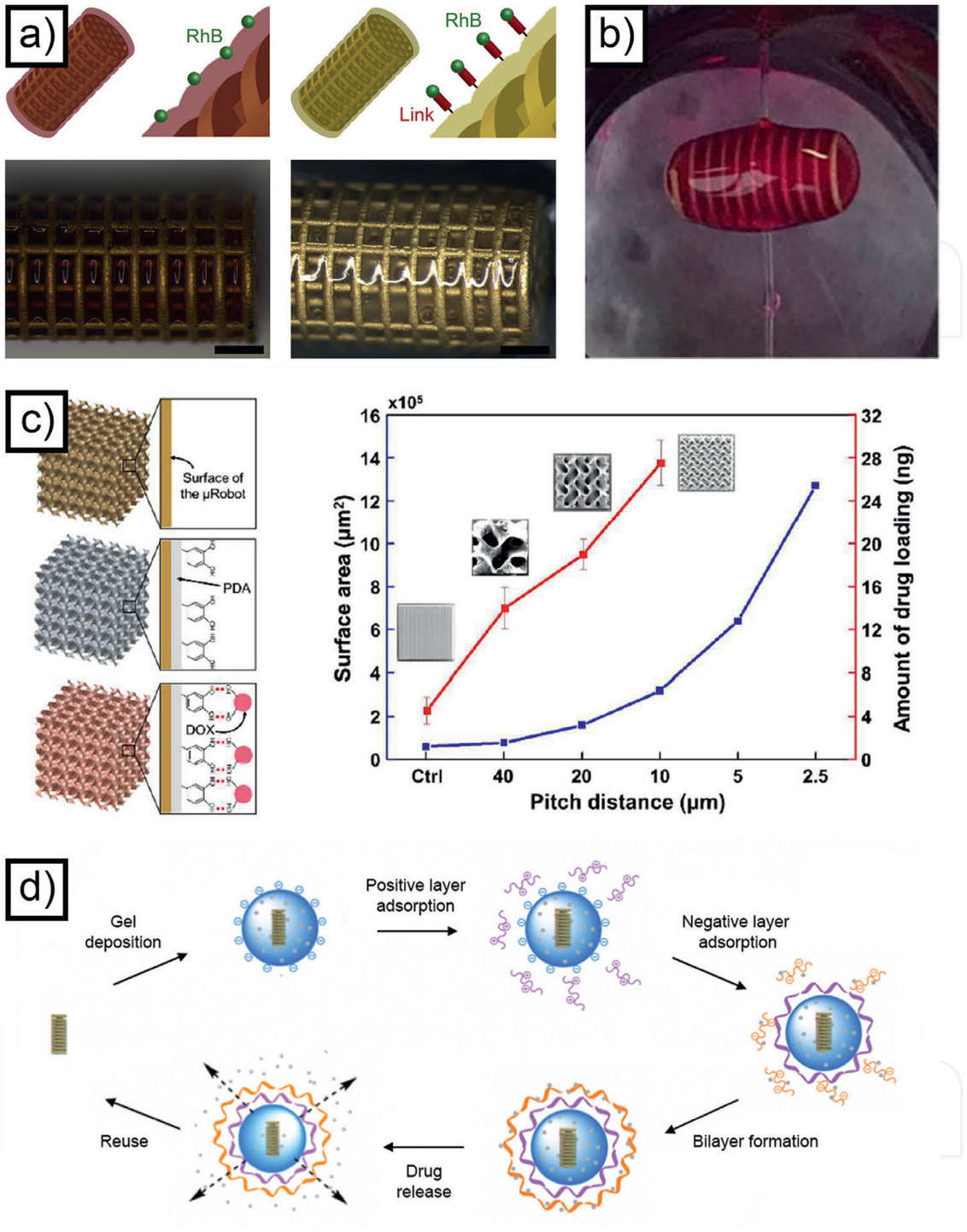

Figure 4.
Physically trapped drug and pH-cleavable drug-hydrogel conjugates applied on magnetically actuated rolling microdevices (a); visual appearance of a magnetically steerable microdevice coated with a reticulated hydrogel physically entrapping a drug (b); schematic of the gyroid surface ABFs drug loading mechanism and the correlated dependence of drug loading on specific surface (c); layer-by-layer hydrogel coating procedure for a magnetically controlled drug releasing device. Reprinted with permission from [33, 60–62].

drug-releasing devices are available. One of the most notable is reported in **Figure 4a** [60]. The authors not only loaded RhB via physical entrapment on their devices, but they also created RhB-alginate conjugates. These structures, created via click chemistry, could release RhB under the influence of a pH variation.

3.3 Surface adsorption

Surface absorption in drug delivery refers to the process where drugs or active pharmaceutical ingredients (APIs) reversibly adhere to the surface of a carrier material. This method involves the weak binding of drugs onto the surface of the microdevices. These interactions can be physical (e.g., van der Waals forces, electrostatic interactions) or chemical (e.g., hydrogen bonding) in nature. This mechanism plays a vital role in DDSs, allowing for controlled drug release and targeted delivery [65]. This method is simple and cost effective, suitable for a variety of drugs and materials. Examples of DDSs utilizing surface absorption include lipid-based nanoparticles [66], polymeric nanoparticles [67] and mesoporous silica nanoparticles [68] among others. These systems leverage surface absorption to achieve efficient drug loading and can be implemented into untethered microdevices. Obviously, in the case of surface adsorption, the guideline that must be followed to increase drug loading is specific surface area maximization. In addition, it is also important to properly functionalize the surface of the devices in order to control the type of bond formed with the drug and tune its adsorption/release kinetics. A notable example of microrobot that bases its drug-loading capability on adsorption and that is very useful to describe these aspects is reported in **Figure 4c** [62]. Zheng et al. manufactured ABFs maximizing the specific area for drug adsorption by introducing a complex gyroid structure and by applying gold nanostars on the surface. In addition, they functionalized the surface with polydopamine in order to enhance the formation of hydrogen bonds between the surface and the drug selected.

3.4 Encapsulation

Nanocarriers can be used to encapsulate and deliver pharmaceuticals that are too toxic, insoluble, rapidly cleared, or unstable as free molecules. These nanocarriers utilize passive or active targeting strategies, depending on the final formulation, to enhance drug delivery effectiveness [69]. The encapsulation technique offers versatility in designing DDSs tailored to specific drugs and applications. Microencapsulation of drug microparticles is indeed a valuable technique for achieving prolonged release of drugs. This approach involves enclosing drug molecules within microspheres or microparticles, typically composed of polymers or liposomes, to control drug release kinetics and improve therapeutic efficacy [70]. From the production point of view, microfabricated fluidic devices that can produce emulsified droplets of uniform size with precisely controlled dimensions and contents are available. These droplets can encapsulate a variety of biological and chemical components, including cells, microgels, beads, hydrogel precursors, polymer initiators, and even other droplets. Encapsulated emulsions are highly desirable for numerous applications because the droplets may serve as miniature reaction vessels, enabling high-throughput reactions at rapid rates while minimizing the use of samples and solvents due to their small size (in the few microns range). The ease of mixing and droplet coalescence facilitates a wide range of on-chip assays with adjustable parameters [71]. The advantage of this method is mainly the protection of the drugs from degradation, enabling controlled and sustained release. Encapsulation is suitable for both hydrophilic and hydrophobic drugs. Some notable examples of microrobots able to carry encapsulated drugs are available in literature. For example, Qiu et al. functionalized the surface of ABFs with temperature sensitive liposomes containing a specific drug [62]. Akolpoglu et al. loaded doxorubicin encapsulated into liposomes on an *Escherichia coli* bacterium, which was guided into complex 3D biological matrices [72].

3.5 Layer-by-layer assembly

The layer-by-layer (LbL) self-assembly technique, developed in the 1990s, is a versatile method for coating nanometer-thick films on various surfaces. This technique relies on the sequential adsorption of oppositely charged components, typically polymers or polyelectrolytes, onto a substrate surface to build up multi-layered thin films [73]. In the case of microdevices, alternating layers of oppositely charged polymers or molecules are deposited onto the surface of the device itself, with drugs incorporated within the layers or released from the assembled structure. In this way, layers characterized by different diffusivities can be superimposed, tuning the release rate of the drug. A representative example is reported in **Figure 4d**. The authors sequentially coated the surface of 3D-printed magnetically steerable devices with layers of chitosan and alginate or poly(allylamine) hydrochloride and alginate [33]. In this way, they successfully confined the drug inside the device and tuned its release.

3.6 Electrospinning

The popularity of electrospinning rose at the end of the twentieth century, as numerous publications began to emerge. This trend continues today, with ongoing research into various applications for electrospun fibers, including drug delivery [74], wound healing [75], tissue engineering [76], textiles and sensors [77]. In recent years, electrospun nanofibers have gained increasing attention due to their unique features, such as biocompatibility and versatility. Incorporating active compounds into nanofibrous meshes has proven to be an efficient method for *in situ* delivery of a wide range of drugs, thereby expanding the potential and applicability of these devices [78]. Electrospinning is a technique where a polymer solution containing the drug is subjected to a high electric field, resulting in the formation of drug-loaded nanofibers that can be deposited onto a microdevice [79]. Pharmacological applications are connected to the use of antibiotics, anti-tumoral drugs, wound healing, cardiovascular diseases and ocular disease. The vast potential of electrospinning offers an exceptional platform for developing innovative DDS that maximize therapeutic benefits while minimizing undesired side effects. The choice of drug and polymer can be easily tailored to specific applications or precise requirements. By adjusting the mechanical properties or the release kinetics, electrospun scaffolds represent a promising new frontier in personalized medicine [78]. For what concerns microrobots, an interesting example of electrospun devices is represented by the work published by Su et al. [80]. They used melt electrospinning writing (MEW) to build magnetically actuated microdevices.

3.7 In situ synthesis

Drugs can also be synthesized directly onto the surface of the microdevice. This approach can enhance drug stability, control release profiles, and improve the efficiency of DDSs. Methods of in-situ synthesis are chemical reactions (polymerization or cross-linking), bioconjugation techniques and surface functionalization. Metal-organic frameworks (MOFs) can be a good example of drug loading at room temperature. Applications of this method are targeted drug delivery, implantable devices, diagnostic devices, and personalized medicine [81].

4. Drug release mechanisms

The term "release mechanism" has been defined in various ways. It is often used to describe the method by which drug molecules are transported or released [82]. Over the past few decades, it has become evident that the method of drug delivery significantly influences its therapeutic effectiveness, impacting various factors such as pharmacokinetics, distribution, pharmacodynamics, metabolism, and toxicity [83]. The most common state-of-the-art methods of drug administration include pills, injections, lotions, and suppositories. Oral dosage forms are typically preferred, as they are simple, painless and can be self-administered. However, drugs administered orally are often degraded in the gastrointestinal tract or not absorbed in sufficient quantities to be effective [84].

One of the biggest challenges in drug delivery for liposomes or other drug carriers like microrobots is to initiate and produce the release of the encapsulated drug specifically at the diseased site. This often involves using external power sources such as ultrasound or radio frequency waves to target areas like solid tumors, allowing for controlled local hyperthermia and phase transitions that increase the release rates precisely where needed [85]. As previously mentioned, external stimuli (ultrasounds, light, heat, etc.) can also be employed to trigger the release from specifically tailored materials able to change their physical or chemical state in response to such stimuli [86].

Controlled release can be defined as a technique by which active compounds are delivered to a target at a specific rate and duration to achieve the desired effect. Various types of mass transport processes can influence the control of drug release from a dosage form [87]. Tunable drug release from microdevices involves various processes that control the rate and extent of drug delivery to the target site. These mechanisms are designed to ensure optimal therapeutic effects while minimizing side effects [88, 89]. It is essential to understand the release mechanisms and physicochemical processes that affect the release rate in order to develop controlled release DDSs.

Numerous processes and events influence the rate of drug diffusion and degradation kinetics, such as polymer-drug interactions [90], drug-drug interactions [91], water absorption [92], and pore closure [93]. Understanding these detailed processes is essential to thoroughly comprehend drug release and control the release rate. Drug release often involves a sequence of processes, including water absorption, hydrolysis, and erosion, all of which are influenced by various factors, adding to the complexity of drug release. The term "release mechanism" is used indifferently in the literature, further complicating the understanding. Various techniques have been employed to study release mechanisms, and the findings vary, which is not surprising given the complexity of drug release [94]. A mechanistic and realistic mathematical description of mass transport in controlled DDSs can be highly beneficial [95]. The most common techniques employed to achieve controlled drug release are discussed in the following sections.

4.1 Diffusion

Release from a device can be considered diffusion controlled when the molecular diffusion of the active agent through any part of the device controls the release rate. The two most relevant types of diffusion-controlled architectures are reservoir and monolithic devices [87]. The solubility of the drug and the geometry of the device determine the type of mathematical equation that must be applied to describe the release. From this point of view, a clear road map for diffusion controlled release modeling has been provided by Siepmann et al., which explained how to identify the

appropriate equations for a specific type of DDS. Their treatise covers reservoir and matrix systems, whether they exhibit an initial excess of the drug or not, and includes different geometries such as slabs, spheres, and cylinders. The assumptions underlying the models and their limitations are also discussed [96].

In general, Fick's laws of diffusion (Eqs. (5) and (6)) are the principles that describe the flux of particles in a medium due to diffusion.

$$J = -D\nabla C \tag{5}$$

$$\frac{\partial C}{\partial t} = D\,\nabla^2 C \tag{6}$$

The molar flux J due to diffusion is proportional to the concentration C gradient multiplied by the diffusion coefficient D. In addition, the evolution over time of the concentration profile can be correlated to the Laplacian of the spatial concentration profile again through the diffusion coefficient. Overall, mass transfer within individual particles typically adheres to the straightforward principles of Fick's diffusion. Even in complex systems, the diffusion coefficient remains a well-defined quantity, rendering qualifiers like "effective," "seeming," or "apparent" unnecessary and potentially misleading [97]. Diffusion-controlled release technologies based on the use of polymeric barriers offer a viable alternative to conventional delivery systems. The two important applications of this technology are complex reservoir systems and monolithic matrix systems [98].

4.1.1 Reservoir devices

In reservoir systems, the drug is contained within a core surrounded by a polymer membrane. The drug diffuses through the membrane at a controlled rate. The thickness and permeability of the membrane are critical factors that determine the rate of drug diffusion. Reservoir-based systems, a subset of microfabricated DDSs, offer unique advantages. These reservoirs, whether external or implanted, create a well-controlled environment for drug formulations, enhancing drug stability and allowing prolonged delivery times. They are versatile, supporting various delivery schemes such as zero-order, pulsatile, and on-demand dosing, unlike the standard sustained release profile. Additionally, the development of reservoir-based systems for targeted delivery in challenging applications (e.g., ocular treatments) has led to promising platforms for patient therapy [99]. From the microrobotics point of view, a good example of reservoir device are the devices obtained through the layer-by-layer process represented in **Figure 4d**. The superimposition of layers able to tune diffusion of chemicals from the hydrogel layers to the external environment optimized drug release and avoided the phenomenon of burst release.

4.1.2 Monolithic devices

As an alternative to reservoir systems, the use of environmentally interactive monolithic devices made with hydrophilic polymers has been proposed and extensively investigated. In these systems, when a solvent enters the drug-entrapping matrix, the polymer swells, allowing the active ingredient to diffuse from the swollen region [100]. The relaxation-controlled desorption is governed by the solvent

concentration at the interface separating the swollen from the unpenetrated polymer. The polymer at this interface relaxes and swells at a constant rate as long as the penetrant concentration at the moving boundary remains constant. Achieving controlled release from this type of device requires a constant surface area and a constant swelling rate of the polymer matrix, as well as a high diffusivity of the entrapped species. These conditions are generally difficult to maintain for extended-release times, as they strongly depend on the evolving interactions among the polymer, the penetrant solvent, and the solute [101]. As an example of the materials employed, polyethylene oxide (PEO) is used for monolithic devices for drug release [98]. As microrobotic examples, the devices represented in **Figure 4a** and **b** can be considered highly significant. In addition, a peculiar example is the device visible in **Figure 5a**, manufactured by Ye et al. [102]. In this case, the drug doxorubicin (DOX) is simply loaded and released by diffusion, but the microdevices are functionalized with folic acid in order to mediate endocytosis (strongly enhancing drug bioavailability).

4.2 Temperature

These systems often incorporate temperature-sensitive materials and temperature-dependent mechanisms to achieve precise, controlled, and responsive drug release. Biodegradable polymer matrixes such as polyesters and poly(ortho esters) are used in *T*-controlled drug release delivery systems. They degrade geometrically from the surface without inner degradation, since drug release can be controlled by the degradation of the matrix [105, 106]. Thermal-sensitive liposomes for cancer treatment utilize dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), whose transition temperature of 41.5°C is just above body temperature, making it ideal for temperature-triggered drug-release technology. After demonstrating enhanced permeability at the phase transition, this property has been applied in liposomes for drug delivery, in conjunction with hyperthermia (a condition that occurs when the body absorbs or generates more heat than it can release) and as an adjunct to radiation therapy [107, 108]. A good example of untethered microdevices that exploit temperature-sensitive materials to guide drug release is represented by the ABFs realized by Zhou et al. They employed a temperature sensitive hydrogel that increased its swelling rate with increasing temperatures (**Figure 5b**) [103]. Another interesting example is represented by the devices produced by Chen et al. [109]. They manufactured fillable microrobots able to release a drug thanks to a temperature variation.

4.3 pH

Drug pharmacokinetics can be pH-sensitive. For this reason, variations in disease state and drug plasma concentration must be considered when developing DDSs to ensure appropriate dosing for effective treatment. However, pH variations can also be exploited in pH-sensitive drug delivery systems (PSDDS), which are becoming important as they release drugs at specific times according to the pathophysiological needs of the disease. This capability results in improved therapeutic efficacy and patient compliance. PSDDS show promise in treating diseases such as asthma, peptic ulcers, cardiovascular diseases, cancer, and hypertension [110]. Tumors, for example, induce localized acidification of the cellular tissues, which can be exploited as a trigger for pH-sensitive materials.

As representative example, it is useful to discuss state-of-the-art gastrointestinal smart drug delivery. It is obtained by coating a core tablet of the gastric fluid-sensitive drug with a combination of an intestinal fluid-insoluble polymer, like ethyl cellulose,

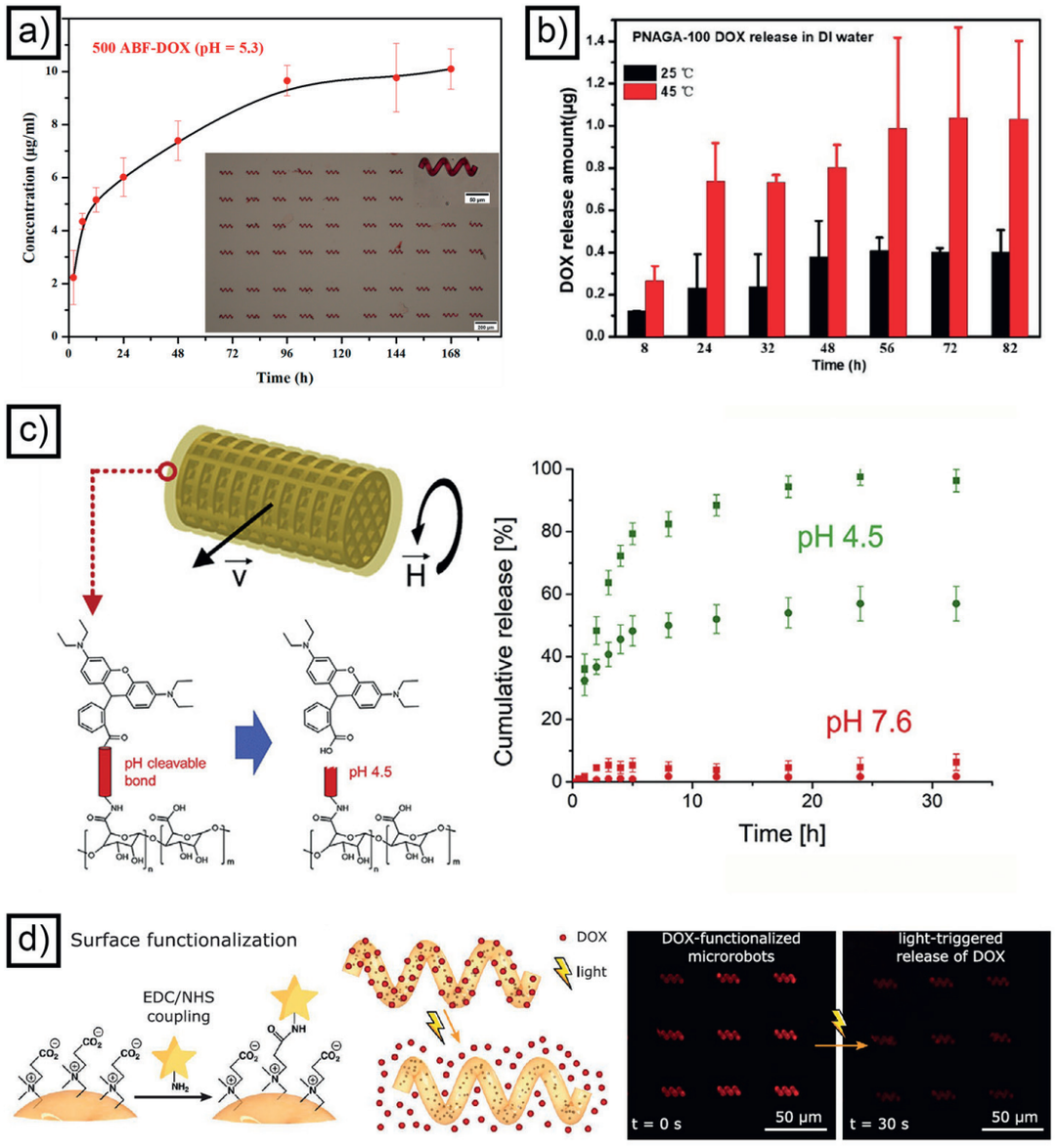

Figure 5.
Drug release curve of magnetic ABFs with folate targeting for drug delivery (a); temperature triggered drug release from hydrogel based microrobots at 25°C and 45°C (b); pH responsive drug-hydrogel conjugates applied on magnetically driven microdevices (c); surface functionalization of microrobots through carboxybetaine functional groups and consequent UV light triggered drug release (d). Reprinted with permission from [60, 102–104].

and an intestinal fluid-soluble polymer, like hydroxylmethyl cellulose phthalate. In the stomach, the coating membrane resists the degrading action of gastric fluid (pH < 3) and the drug molecules are thus protected from the acidic degradation. After gastric emptying, the tablet travels to the small intestine and the intestinal fluid-soluble component in the coating membrane is dissolved away by the intestinal fluid (pH > 7.5), releasing the drug [111]. As representative microrobotic example, the devices loaded with the pH-dependent conjugates reported in **Figure 4a** can be considered. Thanks to the presence of cleavable bonds between the drug and the alginate hydrogel chains, RhB release rate was virtually 0 at pH 7.6. On the contrary, the molecule was efficiently released when the pH fell at 4.5 (**Figure 5c**). Another interesting example has been proposed by Cao et al. [112]. The swarming devices proposed are MOF-based and can release a specific drug as a consequence of pH variations.

4.4 Light

Light-responsiveness is gaining increasing attention due to the potential to develop materials that are sensitive to harmless electromagnetic radiations (primarily in the UV, visible, and near-infrared ranges). These materials can be applied on demand to specific sites in the body. Some light-responsive DDSs are designed for single use, where light triggers an irreversible structural change, releasing the entire dose. Others, capable of undergoing reversible structural changes in response to light and dark cycles, function as multi-switchable carriers, releasing the drug in a pulsatile manner [113]. The development of biocompatible materials for *in vivo* applications, coupled with an improved understanding of photo-regulated solute transport, has expanded the prospects for using photo-responsive materials in drug delivery [114].

As an example, 3D-printed multifunctional zwitterionic microrobots with embedded superparamagnetic iron oxide nanoparticles have been developed, enabling magnetic torque-based swimming locomotion at low Reynolds numbers (**Figure 5d**). Biomolecules were encapsulated in the devices with a single 3D printing step, allowing for the simultaneous incorporation of three fluorescent biomolecules in the microstructure. Surface functionalization with carboxybetaine functional groups enabled UV light-triggered drug release, showcasing controlled drug release capabilities [104]. Another interesting example is the case study reported by Lee et al., who bound gemcitabine (GEM) and doxorubicin (DOX) to the surface of ABFs with light-cleavable bonds. Upon irradiation with infrared light, the devices efficiently released the two cancer treating drugs [115].

4.5 Electric field

Drugs electric field triggered release possibly involves a synergistic process of electrochemical reduction/oxidation and electric-field-driven movement of charged molecules [116]. For example, nanoparticles of a conducting polymer like polypyrrole, loaded with therapeutic pharmaceuticals, can be subcutaneously localized *in vivo* using a temperature-sensitive hydrogel. Subsequently, drug release from the conductive nanoparticles can be controlled by the application of a weak, external DC electric field [116].

4.6 Magnetic field

Effective drug delivery strategies must achieve therapeutic drug concentrations in the specific target area, such as a tumor, while minimizing delivery to off-target tissues [117]. Delivery of drugs to non-target tissues can lead to a range of complications, from mild discomfort to life-threatening side effects [118]. Because biological tissues are minimally responsive to magnetic fields, there has been significant interest in using magnetic nanoparticles in conjunction with applied magnetic fields to selectively control the accumulation and release of drugs in target tissues, thereby minimizing the impact on surrounding tissues [119]. In addition, magnetic actuation is also the preferable propulsion strategy in case of *in-vivo* applications and it can be proficiently coupled with controlled magnetic-induced release.

For example, magnetic fields can be used to induce a highly localized hyperthermia effect at a polymersome membrane, enhancing drug release. This method offers

new possibilities for developing smart delivery systems capable of releasing drugs on demand, thereby improving treatment control [120]. Several inorganic magnetic cores are currently available for potential use in magnetically induced drug delivery [121].

5. Conclusions and outlooks

In the last few decades, extensive experimentation has been conducted by researchers on biomedical microrobots for targeted drug delivery. The results clearly demonstrate the potential of the basic concept behind this family of untethered microdevices: bringing the drug exactly in correspondence with the organ that requires it, avoiding overdosage and side effects for all the remaining organs. The task of building, actuating and controlling drug release of micrometric entities moving at the microscale proved challenging. Nevertheless, many smart approaches have been developed in order to address the issues encountered along the experimental path. Despite these efforts, however, virtually all the models of drug-releasing microrobots currently existing are still in their early stage of preclinical validation. Most of the experiments have been carried out *in-vitro*, with only a few examples of experimentation on animals. Still, the complex environment found in living organisms prevents the research from safely moving to real *in-vivo* tests for active delivery. In particular, untethered microdevices face problems with feedback control over speed and position and from uncertainties on their effective recoverability from the body (or biodegradability in the case of disposable devices). Beyond clinical challenges, also the industrialization of biomedical untethered microrobots offers serious challenges. Most of the available devices have been manufactured only at the lab scale, often using relatively complex and semi-artisanal techniques. Scale-up issues and difficulties in large-scale production may therefore constitute additional barriers to the wide-scale clinical use of untethered biomedical devices. In conclusion, the way toward the adoption of remotely controlled drug delivery devices is still long and full of difficulties. Nevertheless, the potential impact of this technology is so profound that it is still catalyzing research efforts. The possibility of dramatically enhancing drug delivery, especially in critical applications like cancer therapy, will realistically lead, one day, to the successful transfer of drug-releasing microrobots from the laboratory practice to *in-vivo* clinical applications.

Author details

Negar Fouladvari, Roberto Bernasconi and Luca Magagnin*
Dipartimento di Chimica, Materiali e Ingegneria Chimica "Giulio Natta", Politecnico di Milano, Milano, Italy

*Address all correspondence to: luca.magagnin@polimi.it

IntechOpen

References

[1] Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, et al. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023;**9**(6):e17488. Available from: https://www.sciencedirect.com/science/article/pii/S2405844023046960

[2] Park K. Controlled drug delivery systems: Past forward and future back. Journal of Controlled Release. 2014;**190**:3-8

[3] Vikram Singh A, Sitti M. Targeted drug delivery and imaging using mobile milli/microrobots: A promising future towards theranostic pharmaceutical design. Current Pharmaceutical Design. 2016;**22**(11):1418-1428

[4] Chirra HD, Desai TA. Emerging microtechnologies for the development of oral drug delivery devices. Advanced Drug Delivery Reviews. 2012;**64**(14):1569-1578. Available from: https://www.sciencedirect.com/science/article/pii/S0169409X12002578

[5] Pusta A, Casian M, Hosu O, Tertis M, Cristea C. 16 - Microdevice-based aptamer sensors. In: Kesharwani P, editor. Aptamers Engineered Nanocarriers for Cancer Therapy. Cambridge, US: Woodhead Publishing; 2023. pp. 367-402. Available from: https://www.sciencedirect.com/science/article/pii/B9780323858816000063

[6] Kar A, Rout SR, Giri L, Sahebkar A, Kesharwani P, Dandela R. 8 - Aptamer-functionalized nanoparticles for targeted cancer therapy. In: Kesharwani P, editor. Aptamers Engineered Nanocarriers for Cancer Therapy. Cambridge, US: Woodhead Publishing; 2023. pp. 191-218. Available from: https://www.sciencedirect.com/science/article/pii/B9780323858816000208

[7] Elman NM, Patta Y, Scott AW, Masi B, Ho Duc HL, Cima MJ. The next generation of drug-delivery microdevices. Clinical Pharmacology and Therapeutics. 2009;**85**(5):544-547

[8] Varadan VK, Varadan VV. Microsensors, microelectromechanical systems (MEMS), and electronics for smart structures and systems. Smart Materials and Structures. 2000;**9**(6):953

[9] Pusta A, Casian M, Hosu O, Tertis M, Cristea C. Microdevice-based aptamer sensors. In: Aptamers Engineered Nanocarriers for Cancer Therapy. Cambridge, US: Elsevier; 2023. pp. 367-402

[10] Abbott JJ, Nagy Z, Beyeler F, Nelson BJ. Robotics in the small, part I: Microbotics. IEEE Robotics and Automation Magazine. 2007;**14**(2):92-103

[11] Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y, et al. Recent progress in drug delivery. Acta Pharmaceutica Sinica B. 2019;**9**(6):1145-1162. Available from: https://www.sciencedirect.com/science/article/pii/S2211383519306008

[12] Shawgo RS, Richards Grayson AC, Li Y, Cima MJ. BioMEMS for drug delivery. Current Opinion in Solid State and Materials Science. 2002;**6**(4):329-334. Available from: https://www.sciencedirect.com/science/article/pii/S1359028602000323

[13] Singh TRR, Mcmillan H, Mooney K, Alkilani AZ, Donnelly RF. 6 - Microneedles for drug delivery and monitoring. In: Li X(J), Zhou Y, editors. Microfluidic Devices for Biomedical

Applications. Kidlington, UK: Woodhead Publishing; 2013. pp. 185-230. Available from: https://www.sciencedirect.com/science/article/pii/B9780857096975500062

[14] Tonomura O, Maenaka K, Hasebe S. Simplified model-based design of plate-fin microdevices with uniform flow distribution at high flow rates. In: Montastruc L, Negny S, editors. Computer Aided Chemical Engineering. Kyoto, Japan: Elsevier; 2022. pp. 319-324. Available from: https://www.sciencedirect.com/science/article/pii/B9780323958790500540

[15] Ornes S. Medical microrobots have potential in surgery, therapy, imaging, and diagnostics. National Academy of Sciences of the United States of America. 2017;**114**(47):12356-12358

[16] Iacovacci V, Diller E, Ahmed D, Menciassi A. Medical microrobots. Annual Review of Biomedical Engineering. 2024;**26**:561-591

[17] Purcell EM. Life at low Reynolds number. In: Physics and our World: Reissue of the Proceedings of a Symposium in Honor of Victor F Weisskopf. Croydon, UK: World Scientific; 2014. pp. 47-67

[18] Wei T, Li J, Zheng L, Wang C, Li F, Tian H, et al. Development of a cell-loading microrobot with simultaneously improved degradability and mechanical strength for performing In vivo delivery tasks. Advanced Intelligent Systems. 2021;**3**(11):2100052

[19] Ding Y, Qiu F, Casadevall I, Solvas X, Chiu FWY, Nelson BJ, et al. Microfluidic-based droplet and cell manipulations using artificial bacterial flagella. Micromachines (Basel). 2016;**7**(2):25

[20] Bernasconi R, Cuneo F, Carrara E, Chatzipirpiridis G, Hoop M, Chen X, et al. Hard-magnetic cell microscaffolds from electroless coated 3D printed architectures. Materials Horizons. 2018;**5**(4):699-707

[21] Zhuang J, Park B, Sitti M. Propulsion and chemotaxis in bacteria-driven microswimmers. Advanced Science. 2017;**4**(9):1700109

[22] Sitti M. Mobile Microrobotics. Cham, Switzerland: MIT Press; 2017

[23] Halder A, Sun Y. Biocompatible propulsion for biomedical micro/nano robotics. Biosensors & Bioelectronics. 2019;**139**:111334

[24] Sitti M, Wiersma DS. Pros and cons: Magnetic versus optical microrobots. Advanced Materials. 2020;**32**(20):1906766

[25] Wu Z, Lin X, Zou X, Sun J, He Q. Biodegradable protein-based rockets for drug transportation and light-triggered release. ACS Applied Materials & Interfaces. 2015;**7**(1):250-255

[26] Bozuyuk U, Yasa O, Yasa IC, Ceylan H, Kizilel S, Sitti M. Light-triggered drug release from 3D-printed magnetic chitosan microswimmers. ACS Nano. 2018;**12**(9):9617-9625

[27] Buss N, Yasa O, Alapan Y, Akolpoglu MB, Sitti M. Nanoerythrosome-functionalized biohybrid microswimmers. APL Bioengineering. 2020;**4**(2)

[28] Villangca MJ, Palima D, Banas AR, Glückstad J. Light-driven micro-tool equipped with a syringe function. Light: Science & Applications. 2016;**5**(9):e16148-e16148

[29] Puigmartí-Luis J, Pellicer E, Jang B, Chatzipirpiridis G, Sevim S, Chen XZ, et al. Magnetically and chemically propelled nanowire-based

swimmers. In: Magnetic Nano-and Microwires. Cambridge, UK: Elsevier; 2020. pp. 777-799

[30] Reynolds MF, Miskin MZ. Materials for electronically controllable microactuators. MRS Bulletin. 2024;**49**:107-114

[31] Honda T, Arai KI, Ishiyama K. Micro swimming mechanisms propelled by external magnetic fields. IEEE Transactions on Magnetics. 1996;**32**(5):5085-5087

[32] Jeong S, Choi H, Choi J, Yu C, Oh PJ, Park S. Novel electromagnetic actuation (EMA) method for 3-dimensional locomotion of intravascular microrobot. Sensors and Actuators A: Physical. 2010;**157**(1):118-125

[33] Bernasconi R, Pizzetti F, Rossetti A, Butler B, Levi M, Pané S, et al. Layer-by-layer fabrication of hydrogel microsystems for controlled drug delivery from untethered microrobots. Frontiers in Bioengineering and Biotechnology. 2021;**9**:692648

[34] Bernasconi R, Favara N, Fouladvari N, Invernizzi M, Levi M, Pané S, et al. Nanostructured polypyrrole layers implementation on magnetically navigable 3D printed microdevices for targeted gastrointestinal drug delivery. Multifunctional Materials. 2020;**3**(4):045003

[35] Xu R, Xu Q. A survey of recent developments in magnetic microrobots for micro-/nano-manipulation. Micromachines (Basel). 2024;**15**(4):468

[36] Chen R, Folio D. Electromagnetic actuation microrobotic systems. Current Robotics Reports. 2022;**3**(3):119-126

[37] Nocentini S, Parmeggiani C, Martella D, Wiersma DS. Optically driven soft micro robotics. Advanced Optical Materials. 2018;**6**(14):1800207

[38] Xiao Y, Zhang J, Fang B, Zhao X, Hao N. Acoustics-actuated microrobots. Micromachines (Basel). 2022;**13**(3):481

[39] Mourran A, Zhang H, Vinokur R, Möller M. Soft Microrobots Employing Nonequilibrium Actuation Via Plasmonic Heating. Germany; 2017

[40] Rajabasadi F, Schwarz L, Medina-Sánchez M, Schmidt OG. 3D and 4D lithography of untethered microrobots. Progress in Materials Science. 2021;**120**:100808

[41] Chen T, Cai Y, Ren B, Sánchez BJ, Dong R. Intelligent micro/nanorobots based on biotemplate. Materials Horizons. 2024

[42] Wang Z, Mu X, Tan L, Zhong Y, Cheang UK. A rolled-up-based fabrication method of 3D helical microrobots. Front Robot AI. 2022;**9**:1063987

[43] Alcântara C, CJ, Kim S, Lee S, Jang B, Thakolkaran P, Kim J-Y, et al. 3D fabrication of fully iron magnetic microrobots. Small. 2019;(16):**15**:1805006

[44] Bernasconi R, Pané S, Magagnin L. Chapter one - soft microrobotics. In: Magagnin L, Rossi F, editors. Advances in Chemical Engineering. Cambridge, UK: Academic Press; 2021. pp. 1-44. Available from: https://www.sciencedirect.com/science/article/pii/S0065237721000065

[45] Kim S, Lee S, Lee J, Nelson BJ, Zhang L, Choi H. Fabrication and manipulation of ciliary microrobots with non-reciprocal magnetic actuation. Scientific Reports. 2016;**6**(1):30713

[46] Wang X, Cai J, Sun L, Zhang S, Gong D, Li X, et al. Facile fabrication of

magnetic microrobots based on spirulina templates for targeted delivery and synergistic chemo-photothermal therapy. ACS Applied Materials & Interfaces. 2019;**11**(5):4745-4756

[47] Low ZX, Chua YT, Ray BM, Mattia D, Metcalfe IS, Patterson DA. Perspective on 3D printing of separation membranes and comparison to related unconventional fabrication techniques. Journal of Membrane Science. 2017;**523**:596-613. Available from: https://www.sciencedirect.com/science/article/pii/S0376738816304215

[48] Zafar Razzacki S, Thwar PK, Yang M, Ugaz VM, Burns MA. Integrated microsystems for controlled drug delivery. Advanced Drug Delivery Reviews. 2004;**56**(2):185-198. Available from: https://www.sciencedirect.com/science/article/pii/S0169409X03001935

[49] Li J, Pumera M. 3D printing of functional microrobots. Chemical Society Reviews. 2021;**50**(4):2794-2838

[50] Hwang HH, Zhu W, Victorine G, Lawrence N, Chen S. 3D-printing of functional biomedical microdevices via light-and extrusion-based approaches. Small Methods. 2018;**2**(2):1700277

[51] Darmawan BA, Lee SB, Du NV, Go G, Nguyen KT, Lee HS, et al. Self-folded microrobot for active drug delivery and rapid ultrasound-triggered drug release. Sensors and Actuators B: Chemical. 2020;**324**:128752. Available from: https://www.sciencedirect.com/science/article/pii/S0925400520310996

[52] Bernasconi R, Nova A, Aktas B, Pané S, Magagnin L. Inkjet assisted electroforming and collective actuation of disk-shaped magnetic micromotors. Applied Materials Today. 2024;**40**:102365

[53] Qiao S, Ouyang H, Zheng X, Qi C, Ma L. Magnetically actuated hydrogel-based capsule microrobots for intravascular targeted drug delivery. Journal of Materials Chemistry B. 2023;**11**(26):6095-6105

[54] Fox CB, Kim J, Le LV, Nemeth CL, Chirra HD, Desai TA. Micro/nanofabricated platforms for oral drug delivery. Journal of Controlled Release. 2015;**219**:431-444. Available from: https://www.sciencedirect.com/science/article/pii/S0168365915300456

[55] Albayati TM, Alardhi SM, Khalbas AH, Humdi ZJ, Ali NS, Salih IK, et al. Comprehensive review of mesoporous silica nanoparticles: Drug loading, release, and applications as hemostatic agents. ChemistrySelect. 2024;**9**(23):e202400450

[56] Plaza-Oliver M, Santander-Ortega MJ, Lozano MV. Current approaches in lipid-based nanocarriers for oral drug delivery. Drug Delivery and Translational Research. 2021;**11**:471-497

[57] Goldberg M, Gomez-Orellana I. Challenges for the oral delivery of macromolecules. Nature Reviews. Drug Discovery. 2003;**2**(4):289-295

[58] Pant B, Park M, Park SJ. Drug delivery applications of core-sheath nanofibers prepared by coaxial electrospinning: A review. Pharmaceutics. 2019;**11**(7):305

[59] Yokoyama M, Fukushima S, Uehara R, Okamoto K, Kataoka K, Sakurai Y, et al. Characterization of physical entrapment and chemical conjugation of adriamycin in polymeric micelles and their design for in vivo delivery to a solid tumor. Journal of Controlled Release. 1998;**50**(1):79-92. Available from: https://www.sciencedirect.com/science/article/pii/S0168365997001156

[60] Bernasconi R, Mauri E, Rossetti A, Rimondo S, Suriano R, Levi M, et al.

3D integration of pH-cleavable drug-hydrogel conjugates on magnetically driven smart microtransporters. Materials and Design. 2021;**197**:109212

[61] Bernasconi R, Pizzetti F, Rossetti A, Perugini R, Nova A, Levi M, et al. Effect of different physical cross-linkers on drug release from hydrogel layers coated on magnetically steerable 3D-printed microdevices. Technologies (Basel). 2021;**9**(2):43

[62] Zheng S, Hoang MC, Du NV, Go G, Nan M, Darmawan BA, et al. Microrobot with gyroid surface and gold nanostar for high drug loading and near-infrared-triggered chemo-photothermal therapy. Pharmaceutics. 2022;**14**(11):2393

[63] Ke X, Ng VWL, Ono RJ, Chan JMW, Krishnamurthy S, Wang Y, et al. Role of non-covalent and covalent interactions in cargo loading capacity and stability of polymeric micelles. Journal of Controlled Release. 2014;**193**:9-26

[64] Joung YH. Development of implantable medical devices: From an engineering perspective. International Neurourology Journal. 2013;**17**(3):98

[65] Hill TL. Theory of physical adsorption. In: Frankenburg WG, Komarewsky VI, Rideal EK, editors. Advances in Catalysis. Cambridge, UK: Academic Press; 1952. pp. 211-258. Available from: https://www.sciencedirect.com/science/article/pii/S036005640860615X

[66] Chakraborty S, Shukla D, Vuddanda PR, Mishra B, Singh S. Utilization of adsorption technique in the development of oral delivery system of lipid based nanoparticles. Colloids and Surfaces B: Biointerfaces. 2010;**81**(2):563-569. Available from: https://www.sciencedirect.com/science/article/pii/S0927776510004388

[67] He C, Yin L, Tang C, Yin C. Size-dependent absorption mechanism of polymeric nanoparticles for oral delivery of protein drugs. Biomaterials. 2012;**33**(33):8569-8578. Available from: https://www.sciencedirect.com/science/article/pii/S0142961212008587

[68] Vallet-Regí M, Schüth F, Lozano D, Colilla M, Manzano M. Engineering mesoporous silica nanoparticles for drug delivery: Where are we after two decades? Chemical Society Reviews. 2022;**51**(13):5365-5451

[69] Sykes EA, Chen J, Zheng G, Chan WCW. Investigating the impact of nanoparticle size on active and passive tumor targeting efficiency. ACS Nano. 2014;**8**(6):5696-5706

[70] Leong KW, Brott BC, Langer R. Bioerodible polyanhydrides as drug-carrier matrices. I: Characterization, degradation, and release characteristics. Journal of Biomedical Materials Research. 1985;**19**(8):941-955

[71] Desmarais SM, Haagsman HP, Barron AE. Microfabricated devices for biomolecule encapsulation. Electrophoresis. 2012;**33**(17):2639-2649

[72] Akolpoglu MB, Alapan Y, Dogan NO, Baltaci SF, Yasa O, Aybar Tural G, et al. Magnetically steerable bacterial microrobots moving in 3D biological matrices for stimuli-responsive cargo delivery. Science Advances. 2022;**8**(28):eabo6163

[73] Lvov Y, Decher G, Moehwald H. Assembly, structural characterization, and thermal behavior of layer-by-layer deposited ultrathin films of poly (vinyl sulfate) and poly (allylamine). Langmuir. 1993;**9**(2):481-486

[74] Zelkó R, Lamprou DA, Sebe I. Recent Development of Electrospinning for

Drug Delivery, Pharmaceutics. Vol. 12. Basel, Switzerland: MDPI; 2019. p. 5

[75] Sandri G, Rossi S, Bonferoni MC, Caramella C, Ferrari F. Electrospinning technologies in wound dressing applications. In: Boateng J, editor. Therapeutic Dressings and Wound Healing Applications. US: John Wiley and Sons Ltd; 2020. pp. 315-336

[76] Tan GZ, Zhou Y. Electrospinning of biomimetic fibrous scaffolds for tissue engineering: A review. International Journal of Polymeric Materials and Polymeric Biomaterials. 2020;**69**(15):947-960

[77] Mirjalili M, Zohoori S. Review for application of electrospinning and electrospun nanofibers technology in textile industry. Journal of Nanostructure in Chemistry. 2016;**6**:207-213

[78] Luraghi A, Peri F, Moroni L. Electrospinning for drug delivery applications: A review. Journal of Controlled Release. 2021;**334**:463-484. Available from: https://www.sciencedirect.com/science/article/pii/S0168365921001449

[79] Afshari M. Electrospun nanofibers. Cambridge, UK: Woodhead Publishing; 2016

[80] Su Y, Qiu T, Song W, Han X, Sun M, Wang Z, et al. Melt electrospinning writing of magnetic microrobots. Advanced Science. 2021;**8**(3):2003177

[81] Motakef-Kazemi N, Shojaosadati SA, Morsali A. In situ synthesis of a drug-loaded MOF at room temperature. Microporous and Mesoporous Materials. 2014;**186**:73-79. Available from: https://www.sciencedirect.com/science/article/pii/S1387181113005933

[82] Sansdrap P, Moës AJ. In vitro evaluation of the hydrolytic degradation of dispersed and aggregated poly (DL-lactide-co-glycolide) microspheres. Journal of Controlled Release. 1997;**43**(1):47-58

[83] Fenton OS, Olafson KN, Pillai PS, Mitchell MJ, Langer R. Advances in biomaterials for drug delivery. Advanced Materials. 2018;**30**(29):1705328

[84] Ding C, Li Z. A review of drug release mechanisms from nanocarrier systems. Materials Science and Engineering: C. 2017;**76**:1440-1453. Available from: https://www.sciencedirect.com/science/article/pii/S0928493117307282

[85] Needham D, Dewhirst MW. The development and testing of a new temperature-sensitive drug delivery system for the treatment of solid tumors. Advanced Drug Delivery Reviews. 2001;**53**(3):285-305. Available from: https://www.sciencedirect.com/science/article/pii/S0169409X01002332

[86] Sun J, Cai S, Yang W, Leng H, Ge Z, Liu T. Microrobots based on smart materials with their manufacturing methods and applications. Inventions. 2024;**9**(3):67

[87] Fan L, tseng, Singh SK. Controlled Release: A Quantitative Treatment. Vol. 13. Berlin, Germany: Springer Science & Business Media; 2012

[88] Liu D, Wang T, Lu Y. Untethered microrobots for active drug delivery: From rational design to clinical settings. Advanced Healthcare Materials. 2022;**11**(3):2102253

[89] Schmidt CK, Medina-Sánchez M, Edmondson RJ, Schmidt OG. Engineering microrobots for targeted cancer therapies from a medical perspective. Nature Communications. 2020;**11**(1):5618

[90] Blanco MD, Alonso MJ. Development and characterization of protein-loaded poly (lactide-co-glycolide) nanospheres. European Journal of Pharmaceutics and Biopharmaceutics. 1997;**43**(3):287-294

[91] Kang J, Lambert O, Ausborn M, Schwendeman SP. Stability of proteins encapsulated in injectable and biodegradable poly (lactide-co-glycolide)-glucose millicylinders. International Journal of Pharmaceutics. 2008;**357**(1-2):235-243

[92] Desai KGH, Olsen KF, Mallery SR, Stoner GD, Schwendeman SP. Formulation and in vitro-in vivo evaluation of black raspberry extract-loaded PLGA/PLA injectable millicylindrical implants for sustained delivery of chemopreventive anthocyanins. Pharmaceutical Research. 2010;**27**:628-643

[93] Kang J, Schwendeman SP. Pore closing and opening in biodegradable polymers and their effect on the controlled release of proteins. Molecular Pharmaceutics. 2007;**4**(1):104-118

[94] Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems—A review. International Journal of Pharmaceutics. 2011;**415**(1):34-52. Available from: https://www.sciencedirect.com/science/article/pii/S0378517311004807

[95] Baker RW. Controlled Release of Biologically Active Agents. New York, US: John Wiley & Sons; 1987

[96] Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. Journal of Controlled Release. 2012;**161**(2):351-362. Available from: https://www.sciencedirect.com/science/article/pii/S0168365911009588

[97] Titze T, Lauerer A, Heinke L, Chmelik C, Zimmermann NER, Keil FJ, et al. Transport in nanoporous materials including MOFs: The applicability of Fick's laws. Angewandte Chemie International Edition. 2015;**54**(48):14580-14583

[98] Apicella A, Cappello B, Del Nobile MA, La Rotonda MI, Mensitieri G, Nicolais L. Poly(Ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials. 1993;**14**(2):83-90. Available from: https://www.sciencedirect.com/science/article/pii/014296129390215N

[99] Stevenson CL, Santini JT, Langer R. Reservoir-based drug delivery systems utilizing microtechnology. Advanced Drug Delivery Reviews. 2012;**64**(14):1590-1602. Available from: https://www.sciencedirect.com/science/article/pii/S0169409X12000282

[100] Hopfenberg HB, Apicella A, Saleeby DE. Factors affecting water sorption in and solute release from glassy ethylene—Vinyl alcohol copolymers. Journal of Membrane Science. 1981;**8**(3):273-282. Available from: https://www.sciencedirect.com/science/article/pii/S0376738800823157

[101] Korsmeyer RW, Peppas NA. Solute and penetrant diffusion in swellable polymers. III. Drug release from glassy poly(HEMA-co-NVP) copolymers. Journal of Controlled Release. 1984;**1**(2):89-98. Available from: https://www.sciencedirect.com/science/article/pii/0168365984900014

[102] Ye M, Zhou Y, Zhao H, Wang X. Magnetic microrobots with folate targeting for drug delivery. Cyborg and Bionic Systems. 2023;**4**:0019

[103] Zhou Y, Ye M, Zhao H, Wang X. 3D-printed PNAGA thermosensitive

hydrogelbased microrobots: An effective cancer therapy by temperature-triggered drug release. International Journal of Bioprinting. 2023;**9**(3):709

[104] Cabanach P, Pena-Francesch A, Sheehan D, Bozuyuk U, Yasa O, Borros S, et al. Zwitterionic 3D-printed non-immunogenic stealth microrobots. Advanced Materials. 2020;**32**(42):2003013

[105] Heller J. Controlled drug release from poly (ortho esters)—A surface eroding polymer. Journal of Controlled Release. 1985;**2**:167-177

[106] Aso Y, Yoshioka S, Po ALW, Terao T. Effect of temperature on mechanisms of drug release and matrix degradation of poly (d, l-lactide) microspheres. Journal of Controlled Release. 1994;**31**(1):33-39

[107] Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R. Design of liposomes for enhanced local release of drugs by hyperthermia. Science. 1979;**202**(4374):1290-1293

[108] Herman TS. Temperature dependence of adriamycin, cis-diamminedichloroplatinum, bleomycin, and 1, 3-bis (2-chloroethyl)-1-nitrosourea cytotoxicity in vitro. Cancer Research. 1983;**43**(2):517-520

[109] Chen MS, Sun R, Wang R, Zuo Y, Zhou K, Kim J, et al. Fillable magnetic microrobots for drug delivery to cardiac tissues in vitro. Advanced Healthcare Materials. 2024;**13**:2400419

[110] Balamuralidhara V, Pramodkumar TM, Srujana N, Venkatesh MP, Gupta NV, Krishna KL, et al. pH sensitive drug delivery systems: A review. American Journal of Drug Discovery and Development. 2011;**1**(1):24-48

[111] Chien WY. Potential development and new approaches in oral controlled-release drug delivery systems. Drug Development and Industrial Pharmacy. 1983;**9**(7):1291-1330

[112] Cao Q, Zhang Y, Tang Y, Wu C, Wang J, Li D. MOF-based magnetic microrobot swarms for pH-responsive targeted drug delivery. Science China. Chemistry. 2024;**67**(4):1216-1223

[113] Alvarez-Lorenzo C, Bromberg L, Concheiro A. Light-sensitive intelligent drug delivery systems. Photochemistry and Photobiology. 2009;**85**(4):848-860

[114] Lohmann D, Petrak K. Photoactivation and photocontrolled release of bioactive materials. Critical Reviews in Therapeutic Drug Carrier Systems. 1989;**5**(4):263-320

[115] Lee H, Park S. Magnetically actuated helical microrobot with magnetic nanoparticle retrieval and sequential dual-drug release abilities. ACS Applied Materials & Interfaces. 2023;**15**(23):27471-27485

[116] Ge J, Neofytou E, Cahill TJ III, Beygui RE, Zare RN. Drug release from electric-field-responsive nanoparticles. ACS Nano. 2012;**6**(1):227-233

[117] Bae YH, Park K. Targeted drug delivery to tumors: Myths, reality and possibility. Journal of Controlled Release. 2011;**153**:198-205

[118] Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: Short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Boston, MA, US: LWW; 2016

[119] Liu JF, Jang B, Issadore D, Tsourkas A. Use of magnetic fields and nanoparticles to trigger drug release and improve tumor targeting. Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology. 2019;**11**(6):e1571

[120] Oliveira H, Pérez-Andrés E, Thevenot J, Sandre O, Berra E, Lecommandoux S. Magnetic field triggered drug release from polymersomes for cancer therapeutics. Journal of Controlled Release. 2013;**169**(3):165-170. Available from: https://www.sciencedirect.com/science/article/pii/S0168365913000308

[121] Shubayev VI, Pisanic TR II, Jin S. Magnetic nanoparticles for theragnostics. Advanced Drug Delivery Reviews. 2009;**61**(6):467-477