EXPERT OPINION

Microrobots: a new era in ocular drug delivery

Stefano Fusco, Franziska Ullrich, Juho Pokki, George Chatzipirpiridis, Berna Özkale, Kartik M Sivaraman, Olgaç Ergeneman, Salvador Pané & Bradley J Nelson†

Institute of Robotics and Intelligent Systems, ETH Zurich, Zurich, Switzerland

Introduction: Ocular microrobots have the potential to change the way in which we treat a variety of diseases at the anterior and the posterior segments of the eye. Wireless manipulation and positioning of drug delivery magnetic millimeter and submillimeter platforms into the eye constitute a potential route for minimally invasive targeted therapy. However, the field is still in its infancy and faces challenges related to the fabrication, control an interaction with complex biological environments.

Areas covered: This review briefly introduces the complex anatomy and physiology of the eye, which renders limitations to the current treatments of ocular diseases. The topical administration of eye drops, intravitreal injections and drug delivery implants is briefly mentioned together with their drawbacks. The authors also analyze the minimally invasive microrobotic approach as an alternative method and report the recent advancements in the fabrication, control, manipulation and drug delivery.

Expert opinion: Although microrobotics is a young field, a significant amount of work has been developed to face different challenges related to the minimally invasive manipulation of microdevices in the eye. Current research is already at the state of *in vivo* testing for systems and their biocompatibility. It is expected that the general concepts acquired will soon be applied for specific interventions, especially for posterior eye pathologies.

Keywords: eye, functional coatings, magnetic manipulation, microrobots

Expert Opin. Drug Deliv. [Early Online]

1. Introduction

Ophthalmology is a branch of medicine that has evolved through many centuries [1], continuously providing solutions for the treatment of eye diseases. Despite its long tradition and impressive advances, several ocular pathologies still require improvements in the treatment. The reason resides in the complex anatomy and physiology of the eye, which limits the efficacy of certain medical procedures. The eye is a multilayered structure, highly protected from the outer environment on the anterior part and strictly controlled in terms of blood and solute exchanges in the posterior side. The thickness of the eye walls and the surrounding mucous form a thick physical barrier to topical drug administration, while the consistency of the fluids inside the eye globe determines the rate of diffusion of intravitreally injected drugs. A cross-sectional view of the eye (**Figure 1**) [2] depicts three parts:

- An external structure, formed by the sclera, a highly resistant tissue extending to the front of the eye, and a transparent section, the cornea. This multilayer is a clear, avascular and relatively dehydrated tissue, which is mainly negatively charged and poorly permeable to anions. The conjunctiva, the outer protective layer of the eye, is a thin mucous highly vascularized membrane, which is mainly responsible for the elimination of external bodies (like microbes or dirt).

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Article highlights.

- The anatomy and physiology of the eye limit the efficacy of the current drug delivery strategies for anterior and posterior eye pathologies, ranging from topical administration to intravitreal injections. Additional solutions are offered by the use of intravitreal implants for long-term treatments.
- Magnetic microrobots constitute a promising alternative to minimally invasive treatments for drug delivery in the eye. They incorporate the advantages of intravitreal implants into movable and precisely controllable platforms, which can potentially reach any remote area and operate in an intelligent way. Challenges of microrobotics are related to the fabrication, the manipulation and the actuation of these devices inside the body.
- Microrobots have been proposed with different shapes and sizes, ranging from few millimeters to tens of micrometers. Size and shape influence the functionality and the magnetic properties of these devices. Electrodeposition, among the other fabrication techniques, allows controlling the properties of the constituting materials, at low costs and high throughput.
- An electromagnetic manipulation system combined with visual feedback has been used to control the position and the locomotion of microrobots in *in vivo* experiments in rabbit eyes. The trials showed the feasibility of 3D manipulation of magnetic microtubes, and the challenges related to the interaction with the viscoelastic components of the vitreous, affecting their translational and rotational movement.
- Surface treatments have been proposed to enhance the drug delivery abilities of microrobots. Increase of surface area, biocompatibility, interaction with cells and intelligent behaviors are among the features that have been addressed with polymeric coatings. Many other possibilities are offered by the choice of the right material and fabrication techniques.

This box summarizes key points contained in the article.

- An intermediate layer consists of the iris, the ciliary body, the crystalline lens and the choroid. Iris, lens and ciliary body are separated from the cornea by the aqueous humor, a watery fluid, secreted by the ciliary body and mainly responsible for providing nutrients and removing waste. The iris is a thin connective tissue that extends from the ciliary body and surrounds the crystalline lens. This is a transparent biconvex lens, which can change its curvature radius and refractive index depending on the contractions of the ciliary muscle. The choroid is connected to the ciliary body and extends to the posterior segment of the eye, providing oxygen and controlling the temperature and the intraocular pressure. It is a strongly vascularized layer between the sclera and the retina inside the eye globe.
- An inner layer is separated from the rest by the vitreous body and mainly constituted by the posterior part of the choroid and the retina. The vitreous is a transparent, colorless and gelatinous mass, which is mainly composed of water and a fibril network of collagen and hyaluronic acid. The retina consists of photoreceptor cells that receive, pre-process and transmit light signals into the brain through the optic nerve. It is a richly perfused tissue, where multiple neurosensors and connections are resided. The complex structure presents the so-called retinal blood barrier, which regulates the diffusion of substances from the blood into the vitreous and retina.

This review article focuses on the application of microrobots in ophthalmology for ocular drug delivery. Microrobots as a platform for targeted drug delivery are introduced as an innovative alternative to traditional drug administration into the eye. The field of microrobotics combines interdisciplinary engineering sciences, biology and medicine. This paper introduces material science and microfabrication processes required to produce such a microdevice. Additionally, wireless manipulation and control of microrobots in an *in vivo* application is demonstrated. Furthermore, current research about functionalization of microrobots to act as biocompatible nontoxic drug carrier devices is summarized.

2. Treatments of eye diseases and factors limiting their efficacy

Eye diseases are normally classified depending on their location: anterior eye diseases affect the aqueous humor, the cornea, the iris, the ciliary body and the lens. Pathologies derived from bacterial and parasitic infections, corneal abrasions and ulcers are the most common. Aside from infections, the posterior segment of the eye is affected by a variety of disorders such as age-related macular degeneration (AMD), diabetic retinopathies, diabetic macular edema (DME) or retinal vein occlusions (RVO) [3]. The occurrence of these pathologies is quite significant in modern societies with aging population, and they are also relevant in developing countries due to lack of health care and hygiene. Typical treatments involve laser therapy or vitreoretinal surgery.

Drug delivery is a typical solution for most of these pathologies, mainly for the relative low costs and higher compliance from the patient [4]. Ocular drug delivery to the anterior region of the eye is most commonly achieved through topical administration in the form of drops [5]. Nevertheless, precorneal elimination caused by tear fluid turnover and systemic absorption [6] constitutes huge barriers, capable of limiting the penetration through the cornea and the sclera to only 1 – 5% of the active ingredient applied. Aside from that, physical and chemical obstacles reduce the overall efficacy of the treatment [7] and force patients to high-frequency instillations. The deficiency of eye drops has led to considerable research focusing on improved drug delivery systems, especially for pathologies related to the posterior segment of the eye. These include polymer matrices, *in situ* gels [8], emulsions [2], nanoparticles [9] and prodrugs [10] that can prolong

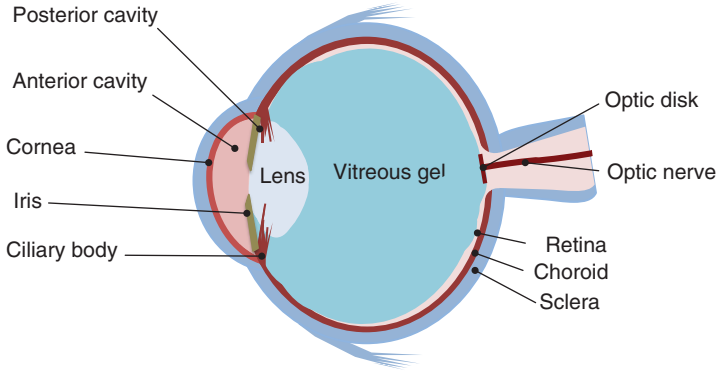

Figure 1. Anatomy of the eye.

the time of residency of the drugs in the eye environment, enhance the drug permeation or produce particular kinetics of release. Recent solutions involved contact lenses as potential long-term drug-eluting platforms [11].

Intravitreal injections can directly bypass physiological barriers and are often used in clinical settings for the treatment of posterior segment infections/diseases. They also provide increased drug level in the targeting zones without causing any side effects. Therapeutic levels can be maintained at lower doses as this route of administration circumvents the blood retinal barrier. However, the limited half-life of drugs in the vitreous cavity necessitates frequent injections, which can induce additional traumas [12], complications such as retinal detachment or endophthalmitis [13], and general patient discomfort [14]. Many researchers have attempted systemic administration of drugs. However, only 1 – 2% of the plasma drug concentration reaches the vitreous humor. This percentage warrants frequent administration or high doses, with nonspecific adsorption by other tissues and toxic effects [15,16].

3. Localized drug delivery and microrobotics

In recent years, microfabrication technologies have provided different solutions for the design and implementation of small carriers. This represents an important step toward the ideal drug delivery system. Devices should be sufficiently miniaturized to reach the disease site but with enough volume to accommodate a relevant dose of drug (tens to hundreds of micrograms to be comparable with the current doses of potent systemic drugs [17]). In addition, it should satisfy biocompatibility and nontoxicity standards throughout their desired time of action. Finally, the device should be trackable and able to release drugs on demand based on external commands or local biochemical changes.

In the last 20 years, a series of intravitreal implants have been developed, some reaching clinical application. The most common cases are related to reservoir implants in which polymeric containers are placed in the posterior segment of the eye by injection or surgery and subsequently removed after use. These devices have been fabricated mostly with silicon, polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA), the first two being permeable for a variety of lipophilic drugs, the last, conversely, being used to reduce the rate of drug diffusion through the implant. Vitrasert® [18] was approved by Food and Drug Administration (FDA) in the 1990s for the treatment of AIDS-related cytomegalovirus retinitis and consists of a 5 mm tube capable of delivering 0.45 mg of ganciclovir over 5 – 8 months. Phase III trials demonstrated a delay in disease progression. However, studies have recognized the occurrence of inflammations related to the insertion of these devices [19]. Retisert® improved the previous design by prolonging the duration of the delivery [20]. Sutured to the sclera for treatment of uveitis, this 5-mm long, 2-mm wide and 1.5-mm thick tablet containing 0.59 mg of fluocinolone acetonide was found to produce significant side effects [21-23], including a 90% risk of cataract or glaucoma. Similar issues were found for Iluvien®, a 3-mm cylindrical tube injected into the vitreous humor using a 25-gauge needle for the treatment of DME [24]. This device has been proven in clinical trials for low-dose long-lasting drug delivery (up to 36 months) but was lately turned down by the FDA and had to be redesigned, based on limited safety results [25]. Similarly targeting DME, I-vation® is a small titanium screw (0.4×0.21 mm) that self-anchors in the sclera delivering triamcinolone acetonide for up to 2 years. The implant's helical coil increased the surface area [26] and used polymer coatings to target biocompatibility and specificity issues.

Other products have addressed the problem of biodegradability by implementing polymeric matrices that change their release rates and accommodate different drugs. Ozurdex® [27,28] (FDA approval in June 2009 for the treatment of macular edema, and in 2010 for the treatment of uveitis) or Lucentis® [29] (FDA approval in 2012) are only two examples of technologies that are nowadays being implemented and receiving continuous attention. In this context, microrobotics for biomedical applications (or biomicrorobotics for short) has emerged as a potential alternative to overcome some of the limits of current treatments.

4. Microrobots for drug delivery in the eye

The field of microrobotics combines aspects of wireless navigation, control, material science, microfabrication, medicine and biology to produce wireless millimeter and submillimeter-sized platforms for targeted therapies. Microrobots have the potential to navigate through bodily fluids and enable basic multiple functions such as sensing, drug delivery and physical support for cells and tissues in parts of the body that are currently inaccessible or too invasive to access [30,31]. The efficacy of the treatments will significantly improve by accurately positioning the devices near the target position, without the need of invasive surgical treatments, and with a sutureless injection. Precise actuation methods, either externally driven by electromagnetic fields, or exploiting physiological triggers (like local acidosis associated with pathological scenarios [32], or temperature gradients related to inflamed sites) would upgrade these systems to a level of intelligence higher than the current commercial products.

The use of microrobots for drug delivery in the eye was first conceived almost 10 years ago [33], when feasibility studies concerning magnetic manipulation and control of microsystems in body fluids were performed. These devices were envisioned as implants to be injected through the durable *pars plana* region into the vitreous cavity by means of a 23-gauge needle and topical anesthesia, and steered toward the retina by means of electromagnetic fields and gradients. Their position could be optically tracked by an ophthalmoscope equipped with a camera pointing to the eye, due to the transparency of the cornea, lens and vitreous.

This work introduced many of the challenges related to biomicrorobotics, including device fabrication, manipulation and control of the position in a fluid environment, and tasks such as sensing and targeted drug delivery. This chapter details the latest development of the methods and materials for fabricating magnetic intraocular microrobots, addresses the advantages and challenges related to manipulation, and reviews some of the recent advances in the fields of functional and smart coatings for microrobotic drug delivery.

5. Design and fabrication of magnetic microrobots

The use of magnetic fields for manoeuvring microrobots in the human body is an advantageous approach due to their biocompatibility and safety (the human body is 'transparent' to magnetic fields, which means that no interactions are present between tissues and quasi-static fields [34]). The topic has been widely researched and is well understood [35-37], and companies such as Stereotaxis, Inc.® and Aeon Scientific® are currently making commercial use of the concept for treatments in the cardiovascular system with tethered catheters.

Magnetic microrobots have been fabricated with different features and shapes, for different medical applications. Bioinspired helical swimmers [38,39] have been proposed for micromanipulation tasks or for destroying kidney stones [40], beads of different sizes have been investigated with the final goal of cardiovascular interventions [41,42], and even hybrid bacteria/artificial nanoactuators have been studied for operation in human blood vessels [43]. Platforms for medical applications in the eye have been presented by our group, with the final aim to provide an alternative treatment for RVOs. The first prototypes consisted of commercial ferromagnetic steel spheres with a diameter of 3 mm, dip coated with an oxygen-sensitive fluorescent coating [44], and proposed as remote optical sensors for hypoxia. The size was chosen as a compromise between minimal invasiveness and high signal-to-noise ratio. The study evaluated the problems of magnetic control and visual tracking in fluidic environments like the vitreous humor.

A more complex design envisioned the use of the platform for simultaneous clot-dissolving drug delivery and retinal vein cannulation [45]. Several techniques can be employed for the microfabrication of 3D magnetic devices with complex shape, including thin film deposition, sputtering, 3D printing [46], stereolithography [47,48], soft lithography [49]. However, obtaining thick, high-quality, well-controlled deposits with these methods are challenging. Electrodeposition is a highly reliable and flexible alternative for these tasks, since it has a fast deposition rate, it does not require special facilities, it is relatively low cost, and is compatible with CMOS circuit fabrication and a variety of organic and inorganic materials [50]. The technique was therefore used for the production of different prototypes of magnetic multifunctional microrobots.

The first generation of devices consisted of multiple electroplated nickel parts assembled together to form a 2.5-mm long, 1.25-mm wide ellipsoid (**Figure 2A**). The parts were produced with a combined process of photolithography (to define selectively the conductive areas on a silicon wafer) and electrodeposition and released by selective etching of a sacrificial layer [51]. Subsequently, they were coated with a titanium dioxide layer or a gold layer for biocompatibility purposes. Their size and shape were selected to optimize the magnetic steering and force generation, and at the same time to provide a large surface for functionalization. The devices, steered in a five degree-of-freedom (DOF) electromagnetic system (see below), were capable of exerting enough forces [51,52] to puncture large blood vessels in a chicken embryo, or detect oxygen concentrations in a fluid environment in a few seconds [53].

A second generation of magnetic microrobots has been recently proposed, specifically for drug delivery applications. Tubular hollow microcylinders (**Figure 2B**) were produced by electroforming galvanostatically cobalt–nickel (CoNi) on a sacrificial mandrel coated with a gold seed layer. Smooth surface finishing was obtained with pulse deposition, while direct current deposition led to nonuniform, pitted deposits. After the deposition, the wire was selectively etched to form a hollow lumen. The tubular shape was preferred because it maximized the volume of magnetic material that could be fitted into a

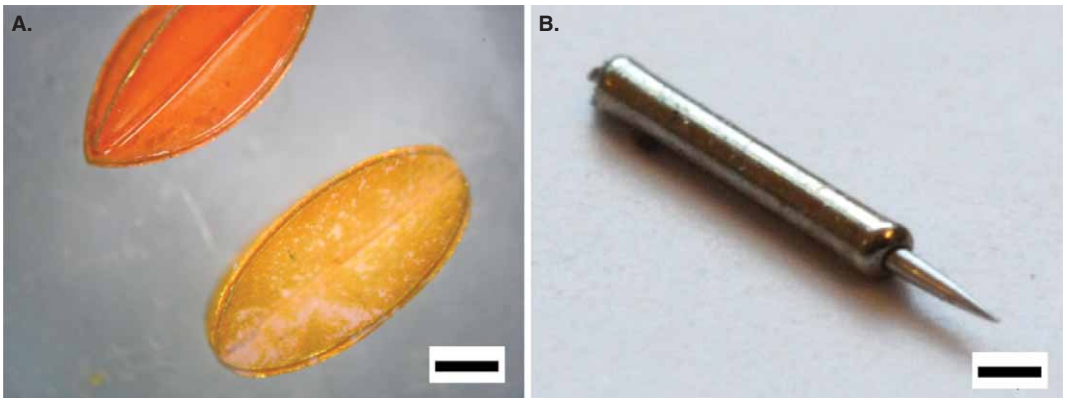

Figure 2. A. First generation of elliptical microrobots (scale bar 500 μm). **B.** Cylindrical microrobots resembling the commercial implants. A microneedle could be implemented during the fabrication (scale bar 300 μm).
A. Reused with permission [53].
B. Reused with permission [77].

23-gauge needle (the outer diameter of the device was 0.6 mm, comparable to the size of the commercial intravitreal implants) and enabled drug loading inside the tube. This new design has been used for *in vivo* experiments of mobility in animal eyes.

6. Mobility experiments with microrobots for minimally invasive intraocular therapies

A five DOF electromagnetic system was specifically designed and implemented for unrestrained magnetic control of untethered microrobots in the eye [51]. The system consists of eight electromagnets in a hemispherical arrangement that accommodates the geometry of a small animal head, neck and shoulders (**Figure 3A**). The OctoMag is designed for an ophthalmoscope equipped with a camera located along the central axis to image microrobots in the eye. By introducing different electric currents into the individual electromagnets, the effective magnetic fields and gradients superpose in the workspace. By adjusting magnetic fields and magnetic field gradients, a wireless soft-magnetic microrobot experiences decoupled torque and force, respectively. Thus, a microrobot can be steered (rotation and translation) in three dimensions, by controlling the currents in the eight coils. The system was recently used for mobility and manipulability studies in lapine vitreous [54]. A microrobot was injected into the eye globe of an anesthetized New Zealand white rabbit using a syringe equipped with a 23-gauge needle, fitting the size constraints for sutureless intravitreal injection. Subsequently, the rabbit's head was placed within the workspace of the electromagnetic manipulation system as illustrated in **Figure 3A**.

After injection, magnetic torques and forces were applied to the intraocular microrobot while an ophthalmoscope with integrated camera observed the workspace and a computer tracked the motion. The microrobot rotated as a result of a rotating magnetic field (0.05 – 2 Hz and magnetic field magnitude of 10 – 40 mT) and translated as a result of applied field gradients (from 0 to 500 mT/m). After experimentation, the microrobot was retracted with a customized 23-gauge magnetic tool.

When a rotating magnetic field was applied, the intravitreal microrobot followed the field rotation with a time delay proportional to the rotational frequency of the field. The time delay between the rotating field and the microrobot is caused by the high viscosity of the vitreous humor, which acts as a damper on the microrobot. **Figure 3B** depicts the rotation of a microrobot around three axes at a constant field rotational frequency in the vitreous humor of a living rabbit eye. It was found that the rotational manoeuvrability of the intravitreal microrobot correlated with the field frequency but not with the investigated field magnitudes.

The *in vivo* experiments showed that the microrobot translated as a function of the applied magnetic field gradient generated by the electromagnetic actuation system. A general increase of translation was observed as a result of increasing field gradients, whereas during several experiments it was observed that the microrobot became entangled in bundles of collagen fibers in the lapine vitreous leading to reduced translational mobility. Nevertheless, the experiments in lapine eyes demonstrate the general feasibility of controlling a microrobot wirelessly in three dimensions inside the vitreous. No signs of immediate inflammation of the lapine eyes were observed, confirming the potential use of this technology for short- and long-term interventions in the eye.

7. Functionalization of the microrobots

The intelligence of the magnetic microrobots resides mainly in the ability of the external user to control their position and movement to the targeted area. However, additional features can be introduced by choosing appropriate materials and methods to produce coatings or surface treatments, which improve the functionalities of the microdevices. Here, we propose three strategies for polymer incorporation on

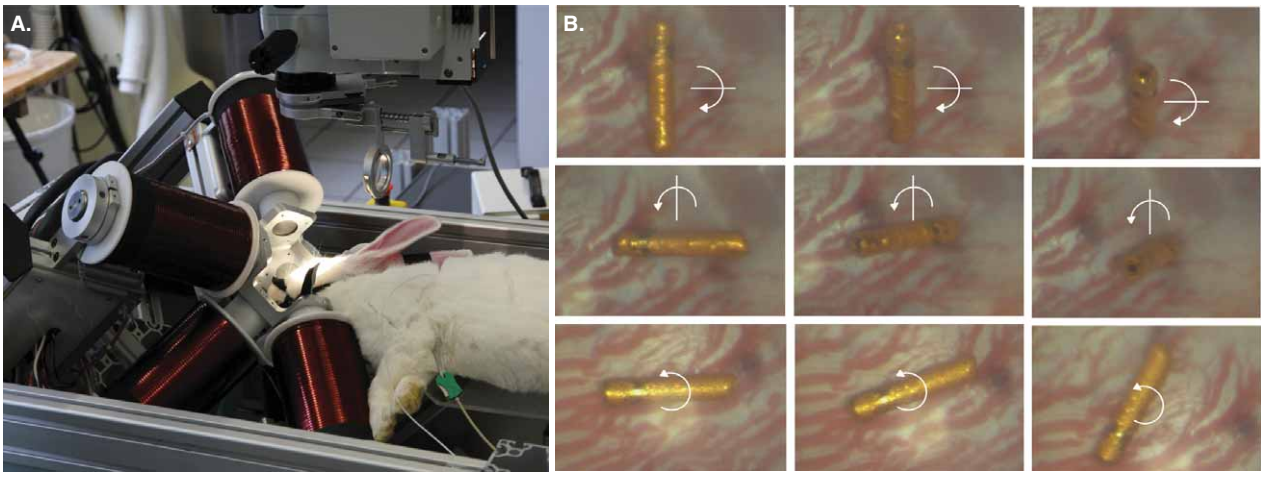

Figure 3. A. The OctoMag system, for the 3D manipulation of microrobots, with the lapine eye (*in vivo*) located in the center of the OctoMag workspace. A microrobot has been injected into the lapine vitreous humor. A disposable planoconcave vitrectomy lens is placed on the eye for increased visibility. **B.** Rotation of the intravitreal microrobot in lapine vitreous (*in vivo*) around different axis.

microrobots; each work provides solutions for specific goals, namely the maximization of the drug loading on the device, the biocompatibility, and the incorporation of triggering mechanisms of drug release. By adjusting material properties these coatings render a microrobot biocompatible and allow for a time-controlled drug release (long-term or a burst).

7.1 Polysulfone porous coatings

At the microscale, the mass transport mechanism is dominated by diffusion, which is geometrically dependent on the surface area in contact with the surroundings. Therefore, increasing this parameter for a microrobot, by means of porous coatings constitutes a smart solution for the maximization of the drug release performances.

Polysulfone (PSU) is a high-performance biocompatible polymer [55], which has been used in blood dialysis membranes [56], and already tested for intraocular drug delivery [57]. Controlled nanoporous coatings (**Figure 4A**) of this material can be easily produced with a selective etching method of $CaCO_3$ nanoparticles, first introduced to filter aqueous dispersions of carbon nanoparticles [58]. The same method was investigated for the functionalization of microdevices [59], as the ones previously described, for drug delivery in the eye, and the drug capability and biocompatibility of the resulting layers were tested in comparison to thick PSU films. Rhodamine B (RhB) was used as model drug, and absorbed into the membranes by dip coating. Loading experiments estimated a quantity encapsulated RhB of 16.5 mg/cm^2, representing a 15-fold increase compared to their nonporous counterpart. Release in PBS revealed a 4-h diffusion kinetics, involving < 40% of the absorbed dye. Considering an ellipsoidal microrobot made by assembling two identical elliptical parts (as the ones seen in **Figure 2A**) each with a major diameter of 1 mm and minor diameter of 0.5 mm, the total RhB loading on a PSU membrane on this microrobot would be around 130 µg, a value that is close to the 190 µg of drug carried by the state-of-the-art intraocular implant, Iluvien®. Cell viability experiments, determined by WST-1 proliferation and cytotoxicity test [60] on a culture of proliferating human foreskin fibroblasts (NDHF) showed only a slight decrease of activity of the cells on porous PSU membranes, compared to bulk films, probably due to traces of solvent. The porous PS was free from adhering and proliferating cells as revealed by LIVE/DEAD fluorescent assays. Considering the fact that proliferation of retinal cells is the cause for eye disorders such as proliferative vitreoretinopathies [61], this can be considered an optimal property of the functional coating.

7.2 Functional poly(pyrrole) coatings

Intrinsically conductive polymers (ICPs) are a unique class of polymers whose polymerization can be achieved through electrodeposition. A doping agent (dopant) is essential for the electrodeposition of these polymers and also to stabilize the polymer backbone by carrying charge in the form of extra electrons [61,62]. Poly(pyrrole) (Ppy) is the most widely researched among ICPs because of its good mechanical stability, ease of synthesis and its well-established biocompatibility in different environments [63,64]. The dopants incorporated into Ppy can move through the matrix on the application of an electric field, and also move between the polymer matrix and the surrounding medium. This mobility of dopants across the polymer–medium interface is largely reversible and is called redox switching [63]. The combination of biocompatibility and redox switching has made Ppy an interesting candidate for immobilizing bioactive molecules on its surface for biosensing and drug delivery and also for tuning its response toward different biological environments [65,66]. A recent work in our group used the modification of the surface and bulk properties

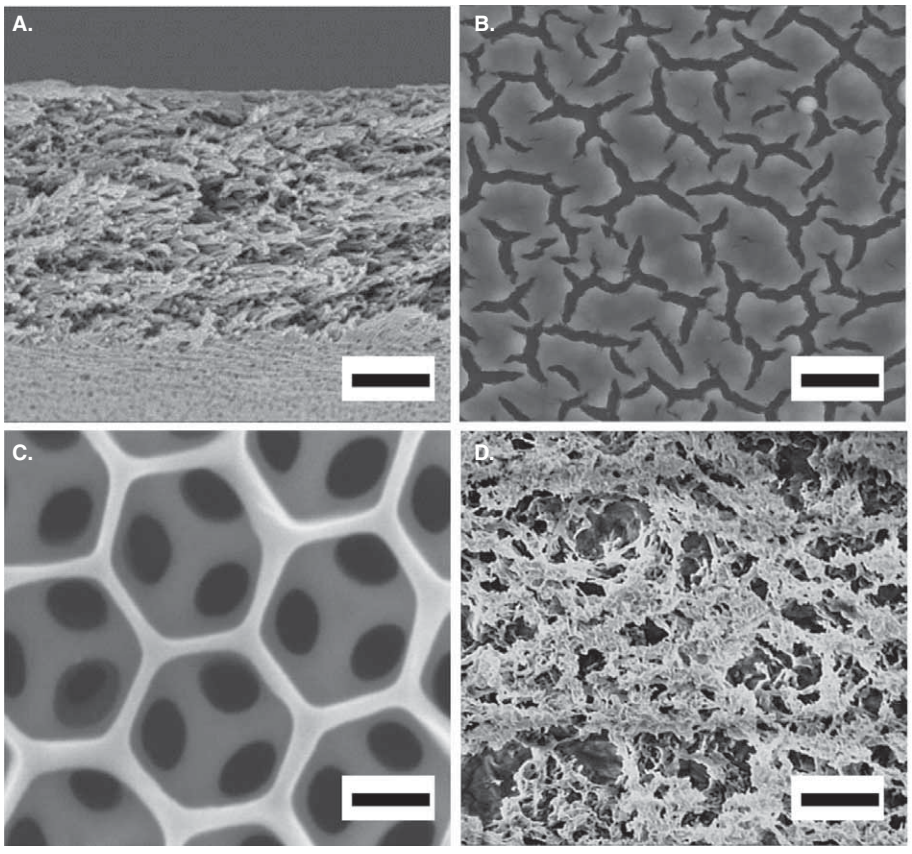

Figure 4. SEM images of different layers for the functionalization of microrobots. A. Cross section of spin coated porous PSU films (scale bar 1 μm). **B.** Cracks formed on the top of a Ppy layer after three cycles of anodization (scale bar 5 μm). **C.** Final porous Ppy nanostructure after chemical removal of the nanospheres (scale bar 200 nm). **D.** Chitosan-electrodeposited matrix for pH responsive drug delivery (scale bar 2 μm).

A. Reused with permission [59].

B. Reused with permission [68].

C. Reused with permission [70].

of Ppy doped with sodium dodecylbenzenesulfonate (NaDBS), and the incorporation into electrodeposited films of PEG, a well-known antifouling material for three purposes:

- Enhance the surface area, by application of a suitable electric potential that could drive the undoping process [67].
- Reduce the adhesion of cells and proteins on the surface of the microrobot [68].
- Trigger on demand release of encapsulated drugs by means of alternating magnetic fields [69].

Redox cycling through cyclic voltammetry was performed in an anodic (positive potential) or in a cathodic range (negative potential). The bulk modification of Ppy by copolymerizing it with PEG and using a lower concentration of NaDBS enabled the incorporation of a high amount of RhB into the matrix. On a composite of thickness 6 μm and surface area of 2.25 cm^2, the amount of RhB incorporated was estimated to be 15.5 μg. Without any external stimulus, 7% of this incorporated RhB was seen to diffuse out of the matrix over 4 h; release was found to be highest for samples undoped anodically, thanks to the presence of cracks and the subsequent increase of surface area (**Figure 4B**). Cathodic samples were instead found to be the least adhesive for fibroblasts, probably due to the charge repulsion between the surface and the matrix proteins. PEG minimized variation in surface wettability between the different treatments, and provided an additional decrease of cell proliferation.

The application of an external alternating magnetic field on Ppy-coated magnetic microrobots, by means of a hollow coil (200 A current at a frequency of 245 kHz) induced eddy currents on the substrate and increased the temperature of about 10°C. The elevated temperatures resulted in a clear increase of the rate of RhB released from the composite. Repeated heating and cooling cycles did not cause any change in the adhesion of Ppy to the substrate, while allowing almost complete release of the loaded model drug.

7.3 Porous honeycomb-like nanostructures

Porous honeycomb-like nanostructures can be used to encapsulate drugs or biomolecules in potential applications of targeted drug delivery. Their drug-loading capacity can be enhanced by fabricating multiple porous layers of the nanostructures (i.e., by increasing the thickness). A sequential fabrication process of the nanostructures out of Ppy was developed based on colloidal lithography and electroplating techniques [70]. First, a template of polystyrene (PS) nanospheres was electrophoretically assembled on the substrate. Subsequently, Ppy was electroplated into the interstitial voids of the PS nanospheres. The final structure was obtained after chemical removal of the PS nanospheres (**Figure 4C**). The method was optimized for best coverage and homogeneity over the substrate. Adsorption and the release characteristics of drug/biomolecules for the nanostructures were measured using RhB. The porous Ppy nanostructures with multiple layers were superior in their RhB loading capacity compared to bulk planar films of Ppy. Moreover, the method is compatible with other materials, and adjustable by the template of nanospheres.

7.4 Smart coatings for microrobotic drug delivery

Chitosan is a polycationic saccharide derived from naturally available chitin, which constitutes an ideal candidate for drug delivery applications in the eye [71]. It is abundant, biocompatible and biodegradable through enzymatic activity [72]; moreover, it has been found to be bioadhesive and acts as a penetration enhancer by opening tight epithelial junctions [73]. Many chitosan properties derive by the presence of the primary amine groups on the repeating units. At low pH, the amines are protonated, allowing chitosan to be soluble in aqueous acid solutions. When the pH exceeds the value of pKa ~ 6.5, the amines are increasingly deprotonated, resulting in a loss of solubility and the formation of stable pH responsive chitosan films. The amine groups also play a central role in the ability of chitosan to be modified with other substances, by means of covalent attachment or physical interaction, to enhance the chemical or mechanical properties of the film (for example, by crosslinking [74]).

Electrodeposition of chitosan exploits the electrophoretic mobility of the chitosan molecules in an electric field and the creation of pH gradients next to the cathode to create stable smart hydrogels on a huge variety of geometries and materials [75,76]. This strategy was used to create functional coatings on the surface of intraocular microrobots, in a completely biologically friendly setup, which avoided harsh physical and chemical conditions [77]. pH responsive hydrogels were formed from chitosan solutions by simple application of a negative potential in a slightly acid (pH 5) water polymer solution (**Figure 4A**). Brilliant green (BG), a common antiseptic for the eye, was added to the bath and incorporated into the growing films. A few minutes of deposition were able to form a swollen hydrogel up to 1 mm thickness. Simple dip-coating processes in NaOH or phosphate salt solutions (sodium trypolyphosphate at pH 5 or 8.5) were used to modify the mechanical and swelling properties of the gel and taken as examples to show the flexibility of the system. Films with a payload of ca. 80 $\mu g/cm^2$ of BG were electrodeposited at 15 A/m^2 in 10 min. Longer process times introduce voids and imperfections and reduce the reproducibility of the measurements but have the potential to increase loading to hundreds of $\mu g/cm^2$. Other parameters such as the applied current density [78] and the concentration of the electrolytes in the bath considerably influence the film structure and composition. Drug release in normal physiological conditions (pH 7.4) could be assured for the duration of 3 – 4 weeks and resulted in the delivery of around half the loaded dye. Different kinetics, from burst releases to almost zero-order profiles could be achieved, depending on the applied dip coating process, due to a physical reorganization of the matrix and a modification of the diffusion pattern in the chitosan films. All the layers exhibited strong pH responsive behavior when immersed at pH 6, a condition similar to that near inflamed tissues [79]. Almost 100% of the loaded amount could be released in a reduced time of action (3 days), due to a complete dissolution of the matrix for almost all cases [80] and a strong swelling caused by electrostatic repulsion among the protonated amine groups.

8. Conclusion

Magnetic microrobots that can be wirelessly steered using external magnetic fields present an exciting new dimension for targeted drug delivery in the eye. In this review, the fabrication, the manipulation and the functionalization of these robotic platforms are reviewed. Due to its ease of use and the variety of magnetic materials that can be used, electrodeposition has been the preferred method to fabricate and functionalize the microrobots. While their core consists of soft magnetic materials deposited in plane or cylindrical shapes, the surface properties can be modulated with biocompatible, drug-eluting coatings. PSU, Ppy and chitosan are only three examples of possible conductive polymers that can be easily implemented, enhancing the drug loading or the sensitivity of these microdevices. Manipulation by means of complex 3D electromagnetic systems has been shown to be effective in fluid environments, and it is currently facing the challenges of *in vivo* experimentation.

9. Expert opinion

The introduction of minimally invasive surgery in the 1980s created a paradigm shift in surgical procedures. These procedures are now linked with a variety of patient-oriented benefits ranging from reduction of recovery time, medical complications, infection risks and post-operative pain to increased quality of care, including preventative care. Health care is now in a position to make a more dramatic leap by integrating newly developed wireless microrobotic technologies to perform precisely targeted, localized drug delivery. Although the

field of medical microrobotics is still in its infancy, recent advances in microfabrication, wireless navigation of microdevices in *in vivo* applications and functionalization of drug-loading devices have been demonstrated. Due to the minimally invasive nature of medical microrobots and the ability to precisely navigate these drug-carrying devices in bodily fluids, there exists great potential to introduce this new technology into medical practice. Although the physics (e.g., fluid dynamics, mechanical and chemical interactions, magnetic properties) of wireless microrobots have been fairly well understood, a number of challenges exist before this vision can be realized. One challenge remaining is the visualization of a medical microrobot inside the human body, especially when utilized in closed vessels or organs. However, to bring microrobots into practice, integration of a magnetic actuation system into the ophthalmic operation room and acceptance from medical staff need to be considered.

One of the most significant achievements pertaining to microrobots for ocular drug delivery has been the ability to precisely actuate and track these devices. This is important because the central premise of using the microrobots has been the reduction in the therapeutic load due to the ability to precisely maneuver them to the location of the pathology. Microrobots would eliminate the need for a vitrectomy, and, in case of an adverse reaction, enable the removal of the microrobot, which is currently not possible with immobile intraocular implants.

The design of a microrobotic platform for drug delivery in the eye faces three main challenges, namely fabrication of the microdevices, wireless manipulation and functionality. Significant advances in the MEMs technology in the last 20 years have allowed the production of different microstructures, with tailored sizes and shapes. Electrodeposition has thus far emerged as the preferred method due to its versatility in terms of the magnetic materials that can be used. The emergence of 3D laser lithography systems in combination with electrodeposition and other techniques such as physical vapor deposition and chemical vapor deposition would allow the high-throughput fabrication of more complicated shapes and smaller sizes of the microrobot that can potentially be operated in the confined spaces of the anterior segment of the eye as well [81,82]. Manipulation of microstructures by means of electromagnetic systems is now a mature field. From simple hard magnets, moved by an operator, we are now at the stage to have automatic navigation systems, which are able to guide precisely and track the position of different entities, in a human size workspace [51,83]. The first *in vivo* tests are currently being performed to support the commercialization of these setups in the field of medical robotics.

The use of surface coatings provides a promising method to enhance the properties of these platforms. The simplicity of synthesizing these coatings, the ability to tune their porosity to incorporate therapeutically relevant amount of drugs, and the ease of integrating them onto the microrobot platform are obvious advantages. Depending on the material used, different drug release profiles can be achieved. Slowly erodible chitosan films are good candidates for long-term treatments of retinal pathologies such as AMD and DME. Moreover, their intrinsic intelligence could be used to actuate faster release on demand. Alternatively, burst releases from Ppy or PSU could potentially benefit patients with RVO, for which to date no effective clinical treatment exists. Various treatment methods for RVO have been proposed and attempted. However, due to excessive postoperative complications or inconclusive clinical trials of other methods, prolonged local intravenous thrombolysis (i.e., clot dissolution) with tissue plasminogen activator (t-PA) injection is currently considered the most promising treatment for RVO [84]. The combination of precise wireless position and burst release of t-PA from a porous outer layer of an intraocular microrobot could obviate the need for the extremely high-risk strategy of cannulating the retinal vessels to insert drugs.

One of the major hurdles on using microrobots for ocular drug delivery has been determining the biocompatibility of the materials being used, especially metallic materials. Conventionally, contact between metals and ocular structures is largely restricted to the use of titanium or stainless steel instruments during invasive surgeries, with the acute ocular toxicity of both metals being negligible. The long-term biocompatibility of intrascleral Ti tacks in rabbit eyes has been reported, as has been the short-term biocompatibility of nitinol (nickel–titanium alloy) clips as a suitable replacement for sutures in anterior segment surgery in mini-pig eyes [85]. Since biocompatibility is a complex phenomenon that is acutely affected by the choice of cells or the culturing medium, comparing results across different animal species and different cell lines is not trivial.

Future research in this field will focus on identifying the target diseases that will benefit from intriguing possibility of real-time diagnosis, targeted drug delivery and minimally invasive surgery through a single wirelessly controlled platform.

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Affiliation

Stefano Fusco, Franziska Ullrich, Juho Pokki, George Chatzipirpiridis, Berna Özkale, Kartik M Sivaraman, Olgaç Ergeneman, Salvador Pané & Bradley J Nelson[†]

[†]Author for correspondence

Institute of Robotics and Intelligent Systems, ETH Zurich, Tannenstrasse 3, Zurich, 8037, Switzerland

E-mail: bnelson@ethz.ch