www.ijrps.pharmascope.org

ISSN: 0975-7538
Review Article

Review on Microrobot

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ABSTRACT

Recent progresses in Microrobots are moving us closer to future in which tiny intelligent machine will navigate through out our bodies. Microrobots, a type of drug delivering submarines have revolutionized many aspects. This review presents the recent progress in this field and discusses near-term applications in ophthalmic therapies. These are used for controlled drug delivery as well as for targeted delivery of drugs and various forms of energy (heat, radioactive energy) as in case of branchy therapy. A Microrobot is still in stages of development, these are largely based on micromachining, Micro Electro Mechanical Systems (MEMS) and scanning probe microscopy. Microrobots are typically envisioned as miniature mechatronics systems that utilize MEMS technology to incorporate sensing and actuation onboard.

Keywords: Microrobot; Minimally invasive medicine (MIM); MEMS; drug release and actuation.

INTRODUCTION

The conventional drug delivery system like needles, pills don't support the desirable constant level of drug in the body. There are several actual trails to diminish the risk that the drug level raises to peak. Research also concentrates on much more futuristical devices like drug delivering submarines (Microrobots) (Richard Attere et al., 2002). A promising approach for achieving minimally invasive medicine (MIM) is via Microrobots wirelessly powered by external magnetic fields (Bradley J. Nelson et al., 2010).

Advances in the synthesis of novel pharmacologically active agents together with recent developments in device miniaturization are revolutionizing modern medicine. The delivery of the active agents needs to be protected during their transit to the target action site in the body while maintaining their biological and chemicals properties. Depending on where the drugs will be absorbed (i.e. colon, small intestine, etc), and whether certain natural defense mechanisms need to be passed through such as the blood-brain barrier, the transit time and delivery challenges can be greatly different. Once a drug reaches at its destination, it needs to be released at an appropriate rate for it to be effective.

These Microrobots which act as vehicle must positively impact the rate of absorption, distribution, metabolism, and excretion of the drug or other substances in the body. They have severe restrictions on the materials and production processes that can be used. The drug delivery material must be compatible and bind easily with the drug.

As the targeting and drive forces are further developed, these tiny untethered devices as vehicles could be realistically used for exploring human vasculature, delivery of agents for diagnosis and therapies and also sensing specific biomolecules. Their functions include recognition, locomotion, therapy and clinical validation (Jong-Oh Park et al., 2010).

SWIMMING ROBOTS

A number of robotic swimming methods have been proposed at relatively small scales. Because many of these methods rely on reciprocating motions, they don't scale downwards. Inspired by the flagellar motion of bacteria such as *E.coli*, artificial bacteria flagella (ABF) was developed. These ABF represent the first wireless swimming Microrobots similar in size and geometry to natural bacteria flagella.

A helical swimming robot consists of two parts: a helical tail resembling natural flagella fabricated by the self scrolling of helical nano belts and a soft-magnetic metal head composed of cr/ni/au stacked in thin films (Li Zhang et al., 2009). The tails are 27 to 42 nm thick, and coil into diameters smaller than three microns.

These swimming Microrobots which are similar to bacteria possess the following properties**:**

1. The robot's skeleton is made of a biocompatible and elastic material (PDMS- polydimethylsiloxane).

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Received on: 06-05-2011
Revised on: 27-05-2011
Accepted on: 01-06-2011

2. These are attached to the Polystyrene (PS) microspheres with electrostatic, hydrophobic and Vander wall bonds **(**Michael Berger et al., 2007)**.**

3. The ABFs currently swim at a speed of up to 20 µm, i.e. up to one body length, per second. Nelson expects that it will be possible to increase the speed to more than 100 µm per second. For comparison: E. coli swims at 30 µm per second ("Medical Micro-robots Made As Small As Bacteria", 2009).

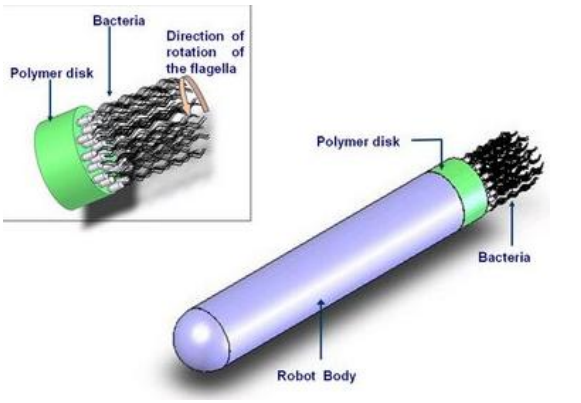

Figure 1: Swimming microrobot

4. The robot has a rectangular body and six legs, three on each end. The front three legs are short (400 micrometers long) and the three rear legs are longer (1200 micrometer long). When the robot's muscle contracts it bends the long front legs. This creates more friction on the rear legs than on the front legs, causing the robot to move.

MEDICAL MICROROBOTS

Micro-robots for medical use can be categorized into two main groups those that are designed for swimming and those that crawl, gripping the inner pipe walls.

The first group might suit medical applications where almost no flow is applied on the robot, while crawling micro-robots may theoretically withstand even massive bloodstream flow present in the human blood vessels. Nevertheless crawling robots that had been designed and fabricated are of impractical sizes for medical use. Another approach is a passive in-a-capsule system, which advances through peristalsis alone (a natural muscular motion). Note that such .systems are thus applicable solely in the gastrointestinal performance [Actuation is applied by an oscillating external magnetic field] while the magnetic field source is located at about 150mm from the robot's location. The robot is capable of crawling up to 9mm/sec if applied into bent or non-bent ventricles having diameters ranging from 3.175mm up to 4 mm (Moshe Shoham et al., 2008)

EXTRUSION AND ENCAPSULATION OF BIOMEDICAL MICROROBOTS

EXTRUSION

The micro-robot extrusion system is a coaxial fluidic channel used to extrude alginate droplets in an oil phase**.** These alginate droplets are the medium that contains and carries the drug**.** By controlling the flow rates of both the alginate stream and the oil phase we are able to vary the size and frequency of the droplets. The picture below shows the basic layout and design of the extrusion manifold.

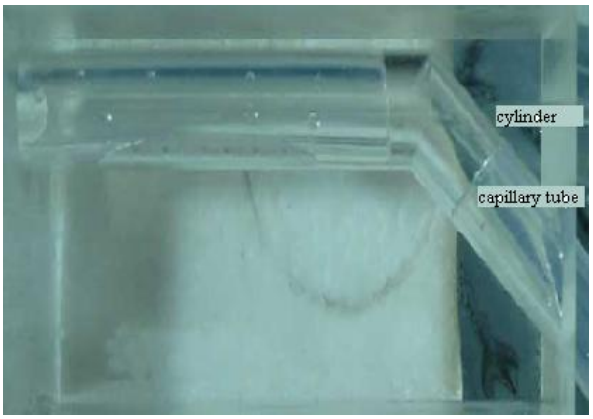

Figure 2: Fluidic manifold with an inner capillary

The larger cylinder contains the oil flow whereas the much smaller capillary tube dispenses the alginate-drug complex. This system allows us to entrap micro-robots within these droplets by feeding them into the capillary tube.

By fine-tuning the flow rates of the oil and alginate-drug complex we are able to create droplets that surround the micro-robots almost perfectly. This is beneficial because it gives us a smooth, clean encapsulated robot.

Figure 3: Robots extruded using this new system

ENCAPSULATION

This portion of the research is devoted to the skin formation around the extruded robot. It is important to incorporate a skin barrier around the alginate-drug complex in order to keep the drug from diffusing while we are transporting or locating the robot. In other words, we want to trap the drug inside the robot until we activate the release.

Encapsulation methods included dip-coating, larger droplet encapsulation, and chemical soaking. These methods would create inconsistent droplets and would limit the potential amount of drug that could be contained within each microrobot Once the micro-robots are extruded they are immediately put through a series of chemical baths or soaks to construct a tough surface

skin that entraps the drug within the robot. The first of these chemical baths is that of Calcium Chloride. Soaking the alginate-based droplet (containing the micro-robot) in this salt causes the calcium chloride to crosslink with the Sodium Alginate thus forming a tough, solid droplet. The droplets are then rinsed and transferred into a Polyethylenimine (PEI) solution where the droplets form a thin protective surface coating. After this skin develops the droplets are again rinsed and transferred into their final soaking in Poly-l-Lysine solution. This solution is hypothesized to soak through the PEI skin and leak into the cross-linking thus strengthening the integrity of the droplet. These three soakings comprise the process of micro-robot capsulation used to prepare the robot for tests and simulated medical procedures.

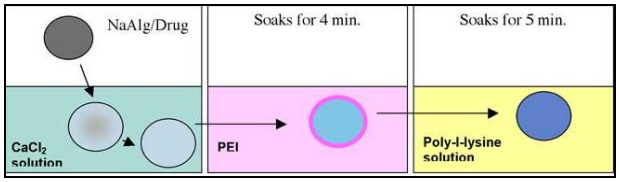

Figure 4: Robot Encapsulation and Skin Formation

MAGNETIC STEERING SYSTEM

This steering system was developed at the Institute of Robotics and Intelligent Systems within the Swiss Federal Institute of Technology. The system they have developed uses two coaxial pairs of magnetic field generating coils in Helmholtz and Maxwell configurations respectively. The Helmholtz configuration creates a uniform magnetic field at the center of the coils. This field induces a magnetic torque on the micro-robot, forcing it to align itself with the field. This part of the system works like a steering wheel by pointing the robot in the desired direction of movement. The Maxwell configuration creates a constant gradient field that induces a force on the robot in the direction of increasing magnetic field. This portion of the system works like the engine by providing movement in the desired direction. A motor is used to control the orientation of the coils and the current in each coil can be adjusted to vary the magnitude of each effect. This system has been used to effectively guide a micro-robot through a small fluidic maze ("Drug delivery mechanisms and extrusion systems biomedical microrobots" 2009).

DRUG ACTUATION AND RELEASE

MAGNETIC PULSING

These Microrobots appears to exhibit a stick-slip motion when actuated by a pulsed magnetic field which is given in a voltage wave form. Two different types of magnetic actuation can be used to move the Microrobot in a reliable fashion. The first is in plane pulsing (IPP), where the magnetic field within the plane of motion is varied, where clamping the magnetic field constant. The second method is out of plane pulsing (OPP), where the magnetic field within the plane of motion is held constant, but the magnetic field is varied. During motion the robots moves by rocking forward and backward around a steady state angle.

This possible means of excitation and triggered release involves the use of a pulsing magnetic field to stimulate the micro-robot structure thus allowing drug to diffuse out of the weakened droplet skin. One specific experiment used two permanent magnets on opposite ends of a rotating rod. The rotational velocity of the rod directly relates to the period of oscillation for the magnetic field. The samples containing the micro-robots are positioned in the center of these spinning magnets. This experiment showed some successful drug release but not in the manner we expected. The release patterns were somewhat sporadic and reflected the oscillatory motion of the magnetic field.

Other ideas involving the use of oscillating magnetic fields are currently being considered. Some ideas involve the use of a stronger magnetic pulse, higher-frequency oscillations, or robots engineered to respond mechanically to a pulsing B-field. (Oliver Brock et al., 2009)

ULTRA SOUND AND ULTRASONIC CAVITATION

This potential mechanism primarily focuses on the use of ultrasound as a means for stimulating fluidic drug release. Ultrasound could be used to cause resonance in the micro-robot thus causing the robot droplet to rupture and release stored drug. It can also be used to induce ultrasonic cavitation (the rapid formation and deformation of micro-scale gas bubbles) to deplete the robots protective skin and allow drug to diffuse outwards into the surrounding fluid.

At this point, only the latter has been experimentally studied. The use of ultrasound to induce ultrasonic cavitation in the fluid surrounding the droplet has shown accelerated depletion of the protective surface skin and thus accelerated release kinetics. This experimental study analyzed not only the release rate of such a mechanism but also the effect of the skin along with the influence of a ferrite powder and micro-robot core. Ultrasound, as a proposed release mechanism, significantly enhances micro-robot release kinetics over past diffusion methods (Drug delivery mechanisms and extrusion systems biomedical microrobots", 2009)

HYDROGEL AS HYPOTHERMIC ACTUATORS

A Microrobot embedded with Magnetic nanoparticles such as superparamagnetic iron oxide (Fe3O4) is used for propulsion and also hyperthermic actuators. When these are embedded in Nisopropylacrylamide (NIPA) thermo responsive hydrogel, vascular Microrobots capable of changing their size to adapt to various diameters of blood vessels could be synthesized. This type of hydrogel is not only able to reduce size in response to temperature elevations but it can also be used to release possible therapeutic agents previously trapped

within the hydrogel **(**Seyed Nasr Tabatabaei et al., 2009).

Once hydrogel with embedded MNP are placed in an alternating magnetic field, the energy from the magnetic field is dissipated to heat and then transferred from MNP to the hydrogel thus increasing its temperature. Therefore the final goal is to integrate MNP with therapeutic agents in micro-carriers made of NIPA hydrogel that are capable of transiting through the smallest capillaries. These micro-carriers can be navigated towards a target such as a tumor.

Hydrogel micro-carriers can rely on an agglomeration of embedded within hydrogel contrast agents MNP used also for propulsion through an induction of magnetic gradients generated by a clinical MRI system. This allows tracking of the micro-carriers as local distortion of the magnetic field inside the MRI system where the confirmation of homogenous distribution of micro-carriers at the target area prior to drug release is easily feasible (Ste'phane Mornetet al., 2004).

Once micro-carriers are aggregated around target area by means of embolization, AC magnetic field can cause embedded MNP to heat the NIPA hydrogel micro-carriers and as a consequence actuate a drug release sequence. At this time, as a result of reduction in hydrogel micro-carrier volume a fraction of embedded MNP along with therapeutic agents are liberated allowing the micro-carrier to move closer towards the target area. Also released MNP around the target area can proceed further in the capillaries and attach to the target tissue by means of antibodies. This may change the topography cues of the environment and neighboring cells and may influence cell cytoskeleton formation. The resulting nano-bumps and nano-spheres on target cells can encourage the cells to switch from growth to apoptosis (cell's self destruction mechanism) (Berry.C.C et al., 2003).

APPLICATION OF MICROROBOTS

TARGETED THERAPY

Microrobots can be used for the localized delivery of chemical and biological substances, as well as various forms of energy. The following are some therapeutic uses:

Targeted drug delivery can be used to simultaneously increase the concentration of drug in a region of interest and reduce the risk of side effects in the rest of the body. The term targeted drug delivery is sometimes used to refer to therapies that target specific cells or genes, but we use the term here to refer to the targeting of a specific location in the body.

Brachytherapy is the placement of a radioactive source, sometimes referred to as a radioactive seed, near unwanted cells such as a tumor (Devlin PM et al., 2007). The radiated energy results in death of the cells close to the radioactive source.

Stem cells hold enormous potential for future therapies (e.g., regeneration of lost hearing and sight). It is not yet clear how differentiated stem cells will be implanted and fostered invivo in a clinical setting. This may be a task well suited to microrobotic assistance.

THE CIRCULATORY SYSTEM

Nearly every site of the body can be accessed by blood, so the circulatory system is the most important application area in for wireless Microrobots. Some of the most important applications of these include targeted drug delivery, removing plaque(rotational atherectomy), destroying blood clots, acting as stents to maintain blood flow, acting as occlusions intentionally starve a region for nutrition, and administering therapy for aneurysms, carrying of electrodes for electro physiology.

CENTRAL NERVOUS SYSTEM

Microrobots designed to fit through 2.5mm channel could navigate the posterior sub arachnoids space in approximately 50% of the population, where as a device designed to fit through a1.5mm channel would fit in at least 85% of population. Gaining access to the ventricles of the brain from the spine is accomplished by passing through the cerebral aqueduct, which is a lumen with a1-2.2mm internal diameter that is 11.8-18mm long. (Duffner F et al., 2003)

Microrobots have the potential to dramatically affect cancer treatment in the CNS. Neural prostheses and deep brain stimulation are other promising applications for Microrobots that are wirelessly guided to hard-to-reach sites. They can even remain as implants. The brains delicate structure demand appropriate caution in any procedure, and the impact of minimally invasive microrobotic procedures could be profound

URINARY SYSTEM AND THE PROSTATE

The length of the ureter, internal diameter, the oblique angle where the ureter enters the bladder wall, length of the urethra, internal diameter of the urethra, all these values can be used as a guideline for urinary tract Microrobots. They have the potential to improve the treatment of kidney stones (nephrolithotomy)

Microrobots are used in the treatment of the prostate cancer. A Microrobot could carry the radioactive seed to the tumor site without causing the bulk deformations in the prostate that result from the needle. In addition a Microrobot could carry a single radioactive seed to a number of tumor locations, stopping at each site long enough to give the appropriate dosage. Microrobots also offer minimally invasive access to the prostate through the urethra (Kosa G et al., 2007).

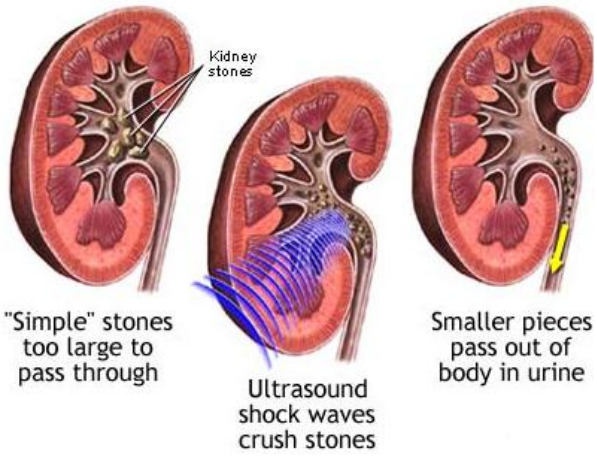

Figure 5: Microrobots in treatment of Nephrolithotomy

THE EYE

RETINAL VEIN OCCLUSIONS

Drug coatings can be used for diffusion-based delivery, and may provide more efficient therapy than Microsystems containing pumps, as diffusion dominates over advection, making transport mechanisms behave differently at small scale. Alternative approach for the development of biomicrorobots utilizing a magnetic platform and functional coatings for remote sensing and targeted drug delivery (Fig. 6).

Figure 6: Microrobot utilizing functional coating; (Right) a bare magnetic microrobot made of thin assembled nickel pieces; (Left) a Microrobot coated with oxygen sensitive film

Luminescence dyes immobilized in coatings can be excited and read out wirelessly for detecting analytes or physical properties. Drugs coated on a carrier can be used for diffusion-based delivery and may provide more efficient therapy than microsystems containing pumps. The proposed devices can be inserted through a small incision in the sclera, and then control within the eye can be accomplished via applied magnetic fields. The eye is unique in that it is possible to observe the vasculature and visually track the microrobot through the pupil (C. Bergeles et al., 2008). It may be more accurate to think of these devices as end-effectors of novel manipulators where magnetic fields replace mechanical links, sensing is performed wirelessly, and system intelligence is located outside of the patient. Robotic assistance in drug delivery will have major benefits. Devices inserted into the aqueous or vitreous cavity bear great potential for drug delivery.

Alternative approach to targeted drug delivery: wireless magnetic microrobots surface coated with drug. The microrobot will be steered to the site of action as it is tracked visually through the pupil, and it will be kept at this position as the drug is released from the microrobot by diffusion.

A. Quantity of Coated Drug

Carrying drug by surface coating becomes more desirable as size is reduced. Consider an assembled microrobot like those shown in Fig.6. The microrobot can be modeled by two elliptical pieces of magnetic material of length 2a, width 2b, and thickness c, and by a circular piece of diameter 2b and thickness c. The microrobot has Vm as volume of magnetic structure and has a volumetric footprint of an ellipsoid of volume Ve .

If we consider a coating of drug that fills in the entire ellipsoidal volumetric footprint of the microrobot (similar to Fig. 7(c)), the volume of drug carried is simply the volume of the ellipsoid minus the volume of the magnetic structure

$$Vf = Ve - Vm$$

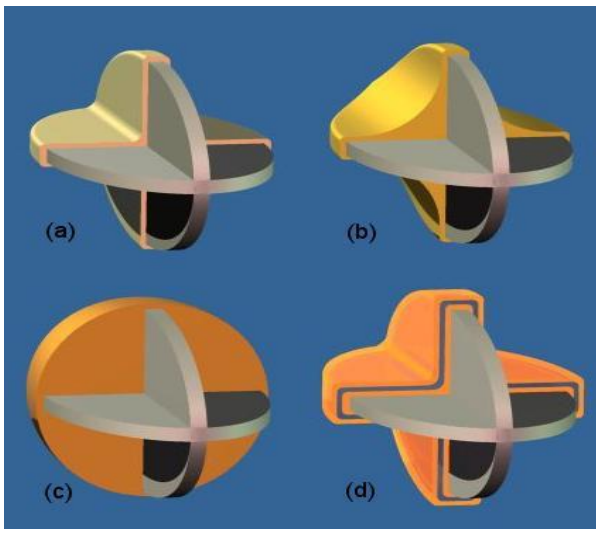

Figure 7: Drug coatings can range from thin surface coatings to coatings take advantage; Coatings are shown only at the back part of the microrobot

For even relatively large microrobots, the amount of drug carried on the surface with a single thin coating is comparable to the total volume of the magnetic structure. As the size of the microrobot is reduced, the volume of drug in a single thin coating becomes comparable to the total ellipsoidal volume of the microrobot. In practice, any fabricated reservoir could only amount to a fraction of the total volume of the structure, and the drug would need to be in solution (that is, diluted) in order to be pumped. In order to bind more proteins or drugs onto a microrobot of the same surface area,

multilayer surface coatings or coatings embedded in different base matrices should be developed (Fig. 7(d)). Among others, hydrogels, agarose,starch microcapsulations, polymer matrices, liposomes, and biodegradable needles are widely used for making drug delivery matrices that can hold much more drug due to their material properties (Cao.X et al., 2001)(Park.J.H et al., 2006). These materials can be used to encapsulate drug molecules as an outer coating, enabling multilayer coatings. These multilayer coatings can be used to coat multiple drug types on one microrobot, or used to fine tune delivery times or dosage. Alternatively, embedding drug molecules in a porous matrix facilitates slower diffusion and more drug loading capacity. Controlled release of drugs has been demonstrated using intelligent polymers that respond to stimuli such magnetic fields, ultrasound, temperature, and pH. They enable fine tuning of diffusive drug release.

B. Drug Delivery for Retinal Vein Occlusions

Retinal vein occlusion (RVO) is a common retinovascular disease caused by obstruction of blood flow due to clot formation. Prolonged local intravenous thrombolysis (i.e., clot dissolution) with tissue plasminogen activator (t-PA) injection is the most promising treatment (Shahid.H et al., 2006) Robotic systems have been proposed to assist with retinal vein cannulation, utilizing robot-assisted surgical instruments that pass through a hole in the sclera as in conventional vitreoretinal surgery (Mitchell.B et al., 2007) (Riviere.C.N et al., 2003). We propose an alternative approach to RVO treatment: a wireless magnetic microrobot coated with clot-dissolving t-PA. The microrobot will be steered to the thrombus site as it is tracked visually through the pupil, and will be immobilized in close proximity of the retinal veins.

Immobilization can be achieved by puncturing and docking to a retinal vein (Dogangil.G et al.,2008). Diffusion of t-PA from the surface coating of the microrobot into the clotted region will start clot dissolution. There is strong evidence that t-PA in the preretinal area can diffuse into the retinal vasculature and break clots (Ghazi.N.G et al., 2003). Since t- PA is an enzyme, and the clot dissolution reaction rate depends on enzyme reaction rate, long-term release of t-PA is thought to be more effective than bolus injections (Tameesh.M.K et al., 2004). The proposed delivery mechanism provides drug release without the need for a micropump, and an efficient therapy using small amounts of t-PA over prolonged periods. Moreover, a microrobot is potentially less invasive than other methods, and has the potential to be left in the eye for extended periods of time, even in an outpatient scenario. However, it is not yet known what quantity of t-Pa is required to effectively dissolve a clot using the proposed method.

C. Preliminary Drug Release Experiments

This section presents the results of preliminary drug release experiments using the untethered microrobot and discusses the feasibility of microrobotic drug delivery. A drug substitute is coated on microrobots, the release kinetics is characterized, and the amount of drug that can be coated in a single layer on a microrobot is quantified.

In order to analyze the release kinetics of a diffusion based drug delivery microrobot, in vitro experiments are conducted. As the drug molecule substitute, bovine serum albumin (BSA) was chosen. BSA is a plasma protein that can be used as a blocking agent or added to diluents in numerous biochemical applications. BSA is used because of its stability, its inert nature in many biochemical reactions, its representative molecular size, and its low cost.

Four elliptical microrobot pieces of length 900 µm, width 450 µm, and thickness 50 µm are used as the magnetic platform holding the coating. The pieces are made from electroplated nickel and then coated with titanium for biocompatibility (Dogangil.G et al., 2008). The pieces are sterilized in ethanol and then washed with sterilized distilled water.

Microrobot pieces are placed in different wells of a 96-well culture plate. A sterilized BSA-solution of 3 mg/mL is prepared and labeled with Alexa-Fluor-546 (Molecular Probes) fluorescent marker. This solution is then mixed with sterilized Phosphate Buffered Saline (PBS) in order to create solutions with different concentrations of labeled-BSA molecules. Three of the microrobot pieces are dipped in BSA concentrations of 3 mg/mL, 2 mg/mL, 1 mg/mL, respectively, and one is dipped into a pure PBS solution, which contained no BSA, as a control set. The pieces are left in the solutions to allow the BSA to bind to the microrobot. The surface-coating process is done for 12 hours at room temperature in a humidity chamber.

Coated microrobot pieces are taken from coating wells and placed in new wells filled with 200 µL PBS each. Following that, the florescence intensity is measured in set time intervals for three days using an automated spectrum analyzer (Tecan Infinite 200 Multiwell Plate Reader). In this way, the kinetics of diffusion-based drug delivery with surface-coated microrobots is obtained.

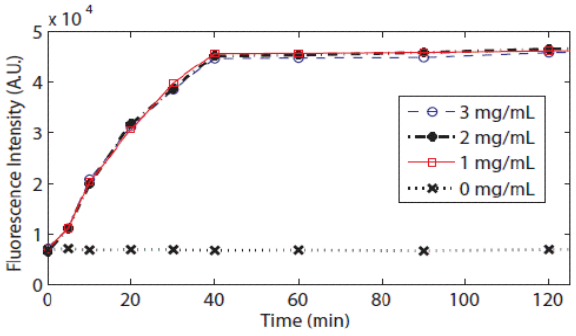

Figure 8: Fluorescence intensity vs time for the release experiment

Fig. 8 quantifies the amount of time required to release the drug through diffusion, and it also gives qualitative information about the kinetics of release. It is clear that the concentration of the coating solution does not affect the amount of drug bound to the surface. This provides strong evidence that the amount of drug will be limited by the surface area of the microrobot.

Next, the amount of BSA released from a single piece is quantified. The release wells of the culture plates are analyzed in the multiwell plate reader for fluorescence and absorbance values. The BSA standard concentration curve is obtained by preparing a Bradford Assay with ten different known concentrations of BSA in 1:2 dilutions, and analyzing this assay for fluorescence and absorbance. The obtained standard curve is used to calibrate the multiwell plate reader. The fluorescence intensity in the release wells is measured and, using the calibration curve, the amount of BSA released is found to be 2.5 ± 0.1 µg (Olgac Ergeneman et al., 2008)

CONCLUSIONS

Mirorobots combines the established theory and techniques of robotics (e.g. motion control, path planning, remote operation or sensor fusion) with the exciting new tools enabled by MEMS technology in order to significantly improve the quality of our lives by virtually eliminate all common diseases in the future, all medical pain and suffering, allow extension of human capabilities. Microrobots in drug delivery technology are still in its infancy stage. This paper presents s regarding the drug extrusion, actuation, release, and application areas of Microrobots. These are promising approach for achieving minimally invasive medicine (MIM) via wirelessly powered by external magnetic fields. Several strategies using wireless magnetic control have been successfully demonstrated to actuate different microrobot designs using complex nonuniform magnetic field gradients. Many theoretical designs have been proposed that look good on paper, but these preliminary designs could change significantly after necessary research, development testing has been completed. Effective collaboration between medical and robotics experts is an important key for the success of this technology of the future.

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