Magnetic Bi-component Millirobot for Targeted Drug Delivery

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INTRODUCTION

The goal of targeted delivery systems for therapeutic agents, e.g, drugs, nucleic acids and cells, is to overcome the limitations of conventional therapeutic strategies by avoiding the side effects of systemic administration. Most delivery systems under investigation, however, such as magnetic nanoparticles and smart triggerable materials, are affected by low controllability and the impossibility of retrieving the delivery system once the therapy has been completed, thus raising toxicity-associated risks [1]. Medical robotics and microsystem technologies can potentially contribute to the development of devices able to navigate a wide network of small-diameter canals and to controllably get in the hard-to-reach areas of the human body [2]. Several strategies have been proposed for microrobot locomotion and magnetic propulsion has emerged as one of the most promising approaches [3].

This paper deals with the design, prototyping and preliminary testing of a magnetically actuated robot able to navigate through relatively small diameter body canals (spine, urinary system, ovary, etc.), and to perform *in-situ* release of therapeutic agents. A bi-component system was developed, consisting of a carrier, in which the therapeutics are embedded, and a piston. External magnetic fields are used to propel and independently bring the robot components to the neighborhood of the target site, whereas intermagnetic attraction forces, acting when the carrier and the piston are in close proximity, are responsible for the docking between the parts that compress a drug-loaded hydrogel, thus activating drug release.

MATERIALS AND METHODS

The system consists of two millimeter-sized near-neutrally buoyant components (*i.e*. carrier and piston) both containing a spherical permanent magnet (NdFeB N45, 1 mm in diameter) (Fig. 1). The carrier consists of a polydimethylsiloxane shell (PDMS, SYLGARD® 184, Dow Corning) provided with holes to allow drug release and with NdFeB powder (Magnequench MQA-37-11, MolyCorp) embedded in its tip to increase magnetic heterogeneity thus enhancing independent control of the robot components [4]. Navigation of robot components can be performed by using an MRI scanner, a coil system or permanent magnets. The therapeutic strategy is articulated as following: *i*) the carrier is injected into the desired body lumen and navigated to the target site where it keeps its position; *ii*) the piston is subsequently injected, oriented and brought to the target area as well. Thanks to the geometric and magnetic differences between the piston and the carrier, independent control can be accomplished [4]; *iii*) when the distance between the two components falls below a critical threshold, the magnetic attraction between the carrier and the piston prevails over the external control force. Docking, compression of a hydrogel and drug release, occur; *iv*) at the end of the procedure the bi-component robot is magnetically retrieved and extracted from the body.

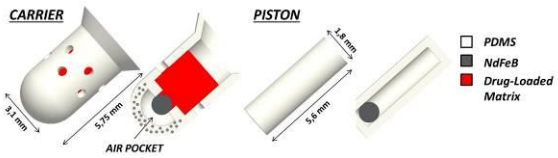

Fig. 1 Bi-component robot design and elements.

In the design of the millirobotic system, the selection of the drug-embedding material is challenging. Hydrogels based on agar and gelatin were selected for their biocompatibility and for the possibility to infuse them not only with drugs, but also with nucleic acids or cells, thus accommodating future therapeutic treatments. Different hydrogel compositions, with different agar concentration (4%, 2%, 1%, 0.75%, 0.5% and 0.25% w/w agar concentration with gelatin concentration fixed at 1% w/w) were fabricated and mechanically tested. In order to identify the best hydrogel composition, finite element model (FEM) simulations were carried out using Abaqus and MATLAB®. The aim was to calculate the deformation of the hydrogel cylinder due to the force exerted by the piston, which corresponds to the dipole-dipole interaction force between the embedded permanent magnets.

An anticancer drug (doxorubicin) commonly exploited for the treatment of different kinds of cancer was embedded into the hydrogel matrix at a concentration of 200 μg/ml. Piston and carrier components were fabricated in PDMS (monomer- curing agent ratio 10:1) by exploiting custom made 3D printed molds and a dedicated setup to orient and accumulate NdFeB powder on the carrier's tip. The polymeric shell components were assembled by embedding the permanent magnets; then, 10 μL of "hydrogel+drug" solution were injected into the carrier and let solidify *in situ* (Fig. 2).

Finally, the correct operation of the proposed platform was evaluated through magnetic locomotion, docking and drug release tests. The amount of doxorubicin

released by different prototypes (n=3) robot was assessed quantitatively through spectrophotometric analysis. *In vitro* tests were carried out by evaluating the effects that the devised procedure produced on human bladder cancer cells (T24, ATCC®, HTB-4™), both in the docked and undocked configurations.

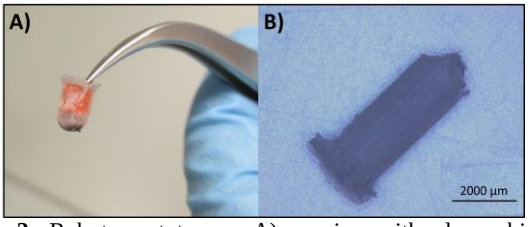

Fig. 2 Robot prototypes: A) carrier with doxorubicin-embedded hydrogel; B) piston.

RESULTS

At the initiation of hydrogel compression, the dipole-dipole attraction force between the embedded permanent magnets is 1.3 mN. FEM simulations revealed that, due to this compression force, a 0.25% agar - 1% gelatin hydrogel produced the best results, undergoing a deformation of about 38%. Further simulations and tests revealed that the embedded doxorubicin does not negatively affect hydrogel behavior, thus leading to the choice of this formulation as drug-loaded matrix. The locomotion of the robot components and the correct operation of the docking procedure were demonstrated in a liquid environment by exploiting a permanent magnets-based control (Fig. 3).

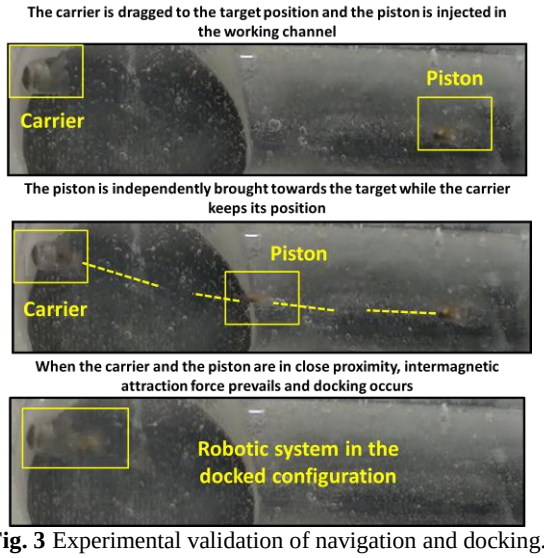

Fig. 3 Experimental validation of navigation and docking.

The efficacy of the drug release procedure was evaluated through spectrophotometric analyses, by measuring the amount of doxorubicin released by each robot prototype after docking. Results demonstrated that the spontaneous release without docking (control samples) is negligible, whereas 6.3±2.4 ng of drug were released by each robot prototype due to docking (Fig. 4A). Procedure efficacy was furtherly demonstrated by treating T24 cells with docking and undocking robots. *In vitro* tests revealed that the amount of doxorubicin released by the carrier is able to produce the desired toxic effect on cancer cells. Both reactive oxygen species (ROS) analysis, carried out 24 h after the docking procedure (fig. 4B), and DNA measurements, carried out 72 h after system testing, confirmed that the docking mechanism is highly effective to activate the drug release, thus damaging cancer cells.

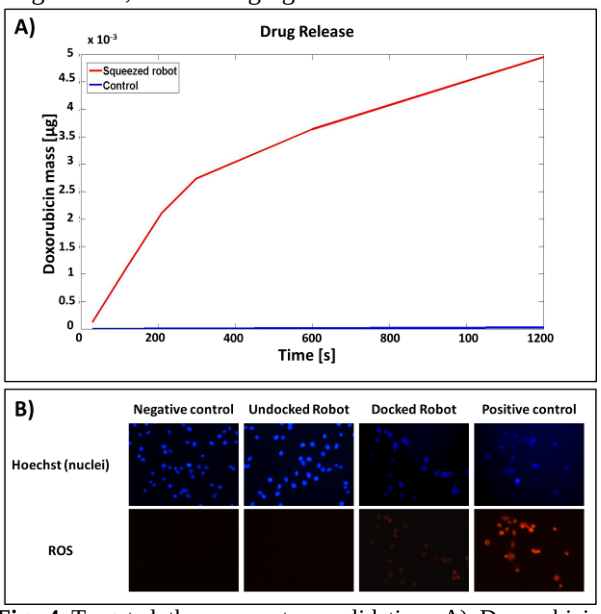

Fig. 4 Targeted therapy system validation. A) Doxorubicin temporal release profile in the docked (squeezed robot) and undocked configuration (control). Measures were performed in triplicate: average curves are reported; B) fluorescence images for the different sample types, 24 h after the treatment (nuclei in blue, ROS production in red). Negative control = no treatment; positive control = 10 µg/mL doxorubicin directly dispersed in the culture medium. Positive control is similar to the "docked robot" condition. Negative control is close to the "undocked robot" condition.

DISCUSSION

This paper reports a novel millirobot concept, enabling reliable targeted therapy in body regions currently reachable only by means of systemic drug administration or low-dexterity instruments. Magnetic locomotion and release tests were carried out, thus demonstrating that the proposed release mechanism, based on controlled squeezing of a drug-loaded matrix, is reliable and efficient and is able to produce a therapeutic effect on cancer cells.

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