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An electric-field responsive microsystem for controllable miniaturised drug delivery applications

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ABSTRACT

A novel MEMS based drug delivery device has been developed, consisting of an array of metallic contacts on silicon and Pyrex glass wafers. The meander structured device creates a uniform electric field which stimulates drug release. An electro-active hydrogel based polymer matrix has also been developed, which responds to an electrical stimulus and shrinks or de-swells on application of an electric field from the fabricated device. Different drug candidates can be encapsulated within the polymer matrix. The de-swelling of the polymer enables the encapsulated drug to be released from the matrix. The gel is able to recover its original size once electric stimulation is ceased. By controlling the applied voltage and its duration, the drug release rate and dose can be precisely controlled. Controlled drug delivery devices may be integrated with sensor technology in combined diagnostic/therapeutic point of care devices.

1. Introduction

Techniques for controlled and targeted drug delivery have drawn increasing attention in both research and clinical applications over the last few decades [1–4]. Achieving responsive, controllable delivery of active compounds is a major challenge. Two different drug release methodologies have been investigated: drug release after a certain time delay and pulsed release in pre-determined sequences [4,5]. Electro-responsive drug delivery, with microfabricated membrane structures or certain hydrogel polymers, can be used to administer time-lagged or pulsed drug release [6–9]. Using three-dimensional high-molecular weight hydrogel networks, encapsulating drugs, electro-responsive controlled drug delivery can be used for prolonged and precisely controlled drug administration. The dose of the drug can be maintained in the desired therapeutic range, and localized delivery of the drug to a particular organ, which is important in a wide variety of applications in medical and pharmaceutical fields, can be achieved [6–8]. Hydrogels have drawn increasing attention over the past two decades in the field of drug delivery due to their ability to swell and de-swell in response to external stimuli. This property can be used to regulate drug release profiles in reservoir-based systems [10]. Hydrogels have been denoted as "smart" materials, as they can respond to different stimuli such as pH, temperature, ionic strength, electric field or specific analyte concentration gradients [11]. In particular, Polymethacrylic acid (PMAA) based hydrogels have been used for the development of electro-sensitive drug delivery systems [12]. The combination of the excellent electrical properties of a novel MEMS based drug delivery microchip and the electro-responsiveness of PMAA hydrogel matrix could generate a high level "on-demand" drug delivery system capable of releasing higher quantities of the drug at pre-determined periods of time.

In this paper, a novel MEMS based drug delivery device, consisting of an array of metallic contacts, is presented. The device creates a uniform electric field which stimulates drug release from a novel PMAA based electro-active hydrogel polymer matrix. The delivery microsystem responds to an electrical stimulus, created by applying a voltage through the meander contact device, and the induced shrinking or de-swelling of the polymer matrix enables the encapsulated drug to be released. This MEMS based drug delivery system could deliver high drug doses in a pulsatile release profile and offers reproducible delivery characteristics – facilitated by the electro-sensitivity of the hydrogel polyelectrolyte, developed specifically for electro-stimulated drug release. The electro-stimulated release mechanism allows a remote-controlled microchip, to actuate the timing, duration, dosage, and even location of drug delivery. It also enables remote, non invasive, repeatable, and reliable switching of the release of the therapeutic agent.

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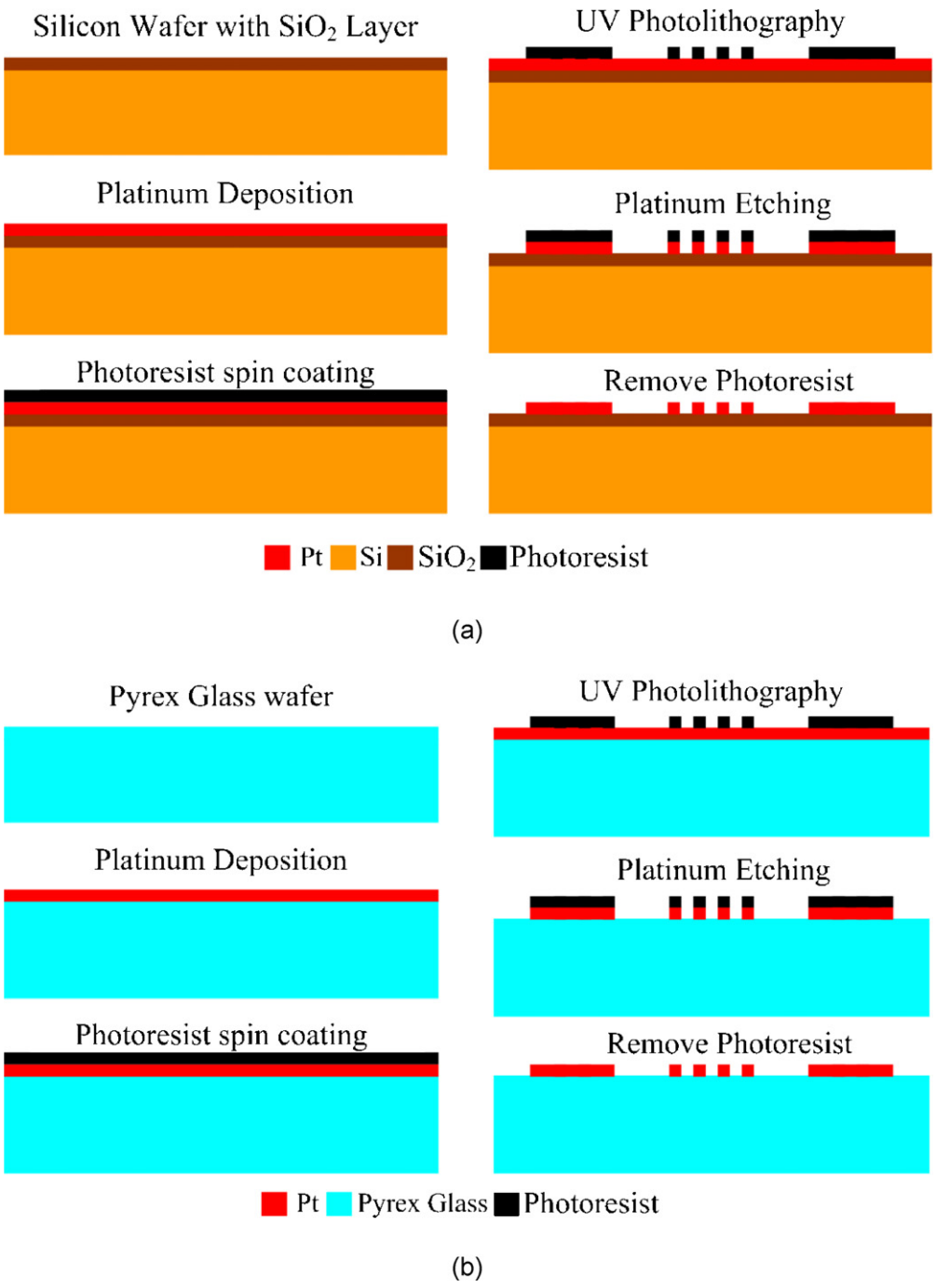

Fig. 1. Fabrication process of platinum based drug delivery microsystem (a) on silicon substrate and (b) on Pyrex glass substrate.

2. Device design and fabrication

The meander tracks were fabricated using sputtered platinum films deposited on silicon wafers and Pyrex glass wafers. The device fabrication process flow is shown in Fig. 1. The silicon wafers have a pre-deposited layer of silicon dioxide of thickness of 1 μm via plasma-enhanced chemical vapor deposition (PECVD). The thickness of the platinum films was about 100 nm. A 10 nm layer of titanium was used as an adhesion layer between the platinum film and the wafer surface. After deposition of the platinum film on a wafer, photoresist was spin coated on to the wafer and patterned using photolithography. Using the patterned photoresist as a mask, the platinum films were patterned using an ion beam etching method to produce the drug delivery devices. The fabrication process for Pyrex glass wafers is as the same as that of the silicon wafers. Metallic meander tracks were designed in widths of 3 μm and 10 μm. The fabricated devices, shown in Fig. 2, have footprints of 240 μm × 250 μm and 700 μm × 700 μm, respectively. Drug delivery sensors with track widths as narrow as 3 μm have been obtained successfully.

The thermal and electric field properties of the device have been simulated using finite element methods (FEM), based on the drug delivery microsystem with a footprint of 700 μm × 700 μm with 36 meander track units. As shown in Fig. 2(b), the dimension of each unit was designed as 10 μm wide and 700 μm long. The simulation result in Fig. 3(a) shows that a uniform electric potential was

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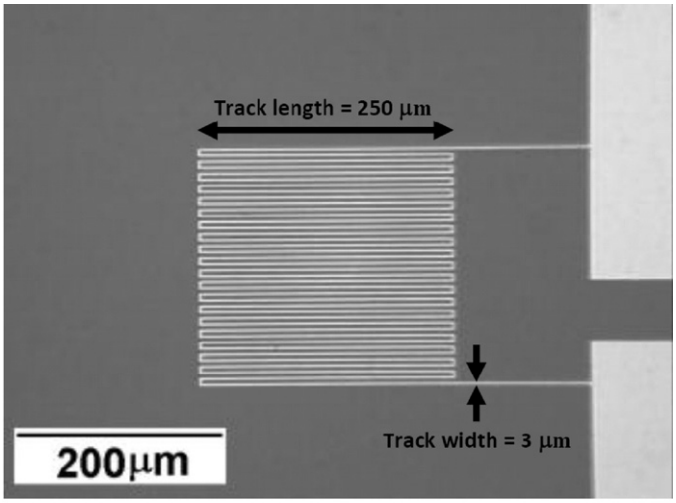
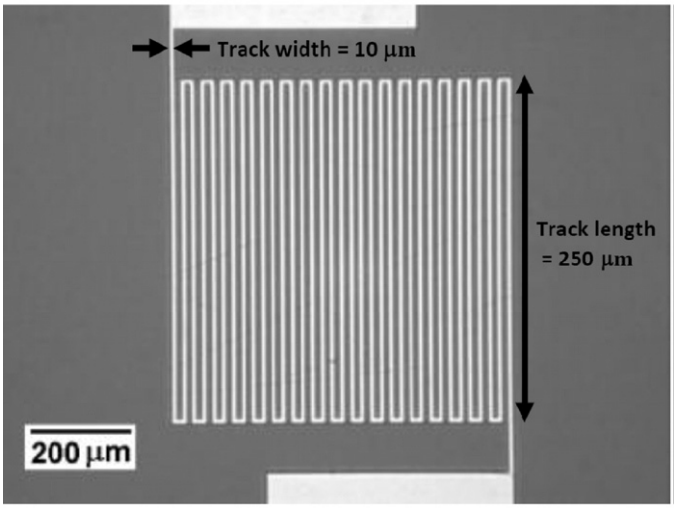


(a)



(b)

Fig. 2. Fabricated drug delivery devices with meander metallic structures in track width of (a) 3 μm, and (b) 10 μm.

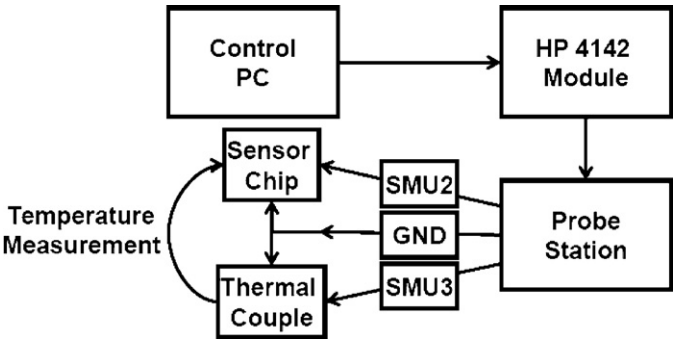


Fig. 4. Schematic set up for thermal property tests.

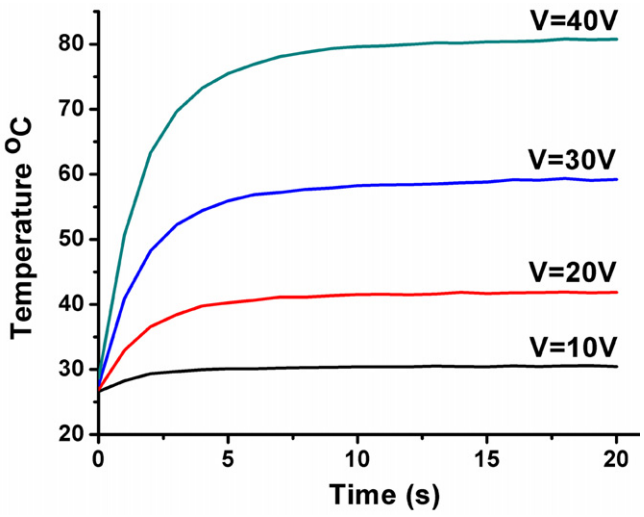
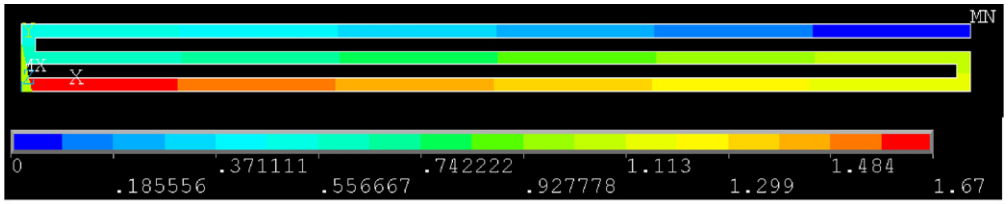
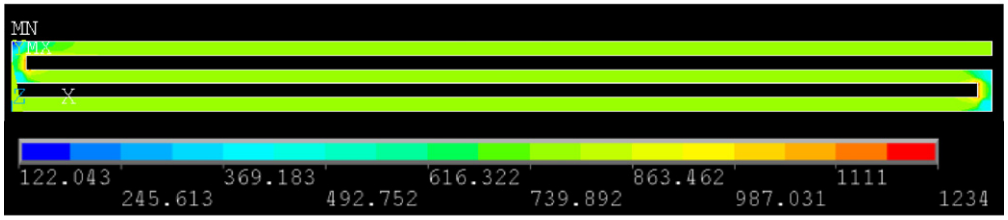


Fig. 5. Thermal property of fabricated devices under different DC voltages.

created along the metallic meander tracks, which resulted in a uniform electric field along the meander metallic contacts (except at the corners of the tracks) shown in Fig. 3(b). In simulations using ANSYS software in electrical–thermal simulation mode, a voltage of 1.67 V was applied to a 3-unit meander metallic contact structure (which would be equivalent to 20 V in the actual fabricated structure of 36 meander units shown in Fig. 2(b)). The thermal properties



(a)



(b)

Fig. 3. FEM simulation results of (a) electric potential and (b) electric field vector summation in a 3-unit metallic meander structure.

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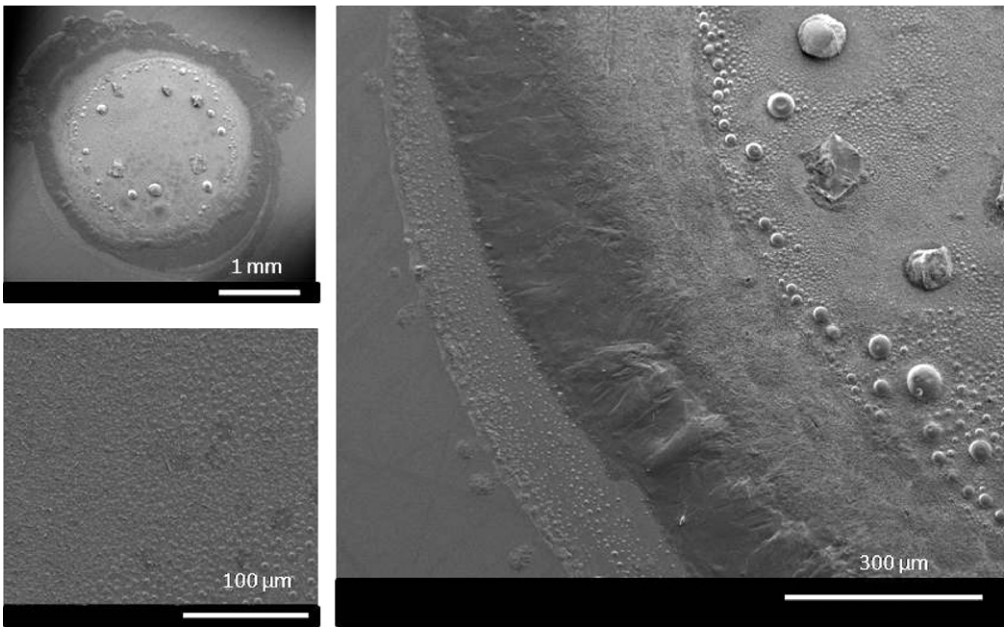

Fig. 6. Scanning Electron Micrograph (SEM) pictures of the PMAA based hydrogel surface.

of the meander structures, under a constant DC bias applied using a probe station coupled to a HP 4142b electrical analyzer (Fig. 4), have been measured using a thermometer (YC-727D, Yu Ching Technology Co. Ltd.). The temperature properties of device under different DC conditions are shown in Fig. 5. These results show that fabricated devices operate at normal body temperature (37 °C) when a DC bias of 20 V is applied to the meander structured device.

3. Optimisation of the hydrogel formulation

Homogenous PMAA hydrogels have been successfully prepared by in situ radical polymerization – directly on the MEMS based microchip – with the aim of developing an efficient, implantable, controlled drug delivery system capable of producing a pulsatile release profile in response to the applied electric field. The hydrogel matrix was optimised for drug release through application of several ON/OFF cycles of the electric voltage to the microchip circuit. Flexible hydrogel matrices were required for this application, since successive swelling and de-swelling upon the ON/OFF application of the electric field would cause cyclical stresses to the polymeric matrix. The flexibility of the polymer matrix is closely related to the swelling capacity. The concentration of cross-linking agent used is the determining factor in gel flexibility. Studies have been performed on the hydrogel structure and swelling properties at the macroscopic level have determined that the optimal cross-linker content for an optimal gel response to the electric field was around 1 mol%, using N,N′-methylene bisacrylamide as the cross-linking agent, which means that the proportion of cross-linker compared to the MAA monomer is 1% in mol. As a consequence, a cross-linker content of 1 mol% was used in this drug delivery application for the electrically triggered drug release. The gel was then prepared by in situ radical polymerization of the gel on the MEMS based microchip. One microliter of the pre-polymerization solution, containing Methacrylic acid (MAA) as a monomer (distilled under vacuum before use), N,N′-Methylenebis(acrylamide) (MBAA) as a cross-linker (1 mol%) and potassium persulfate, used

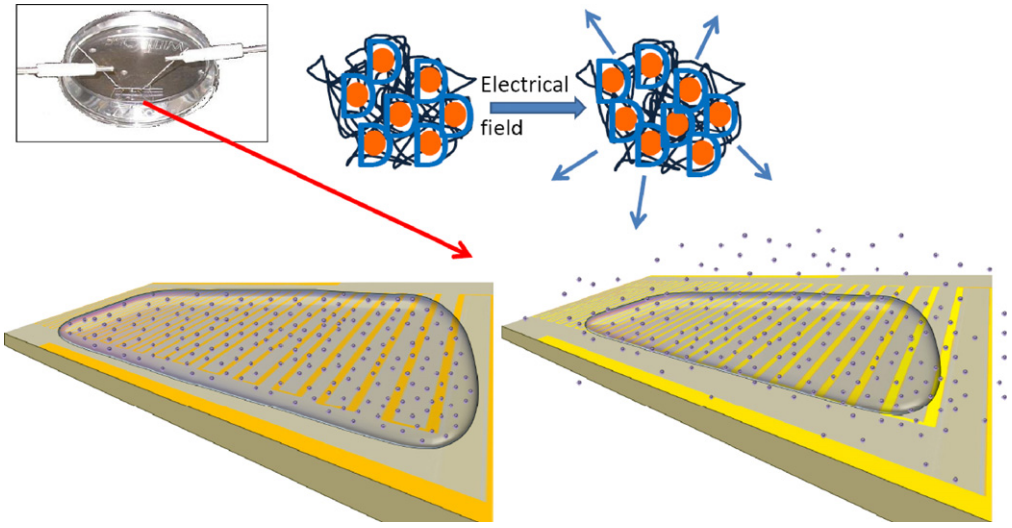

Fig. 7. Schematic of polymer de-swelling drug delivery device due to electronic field.

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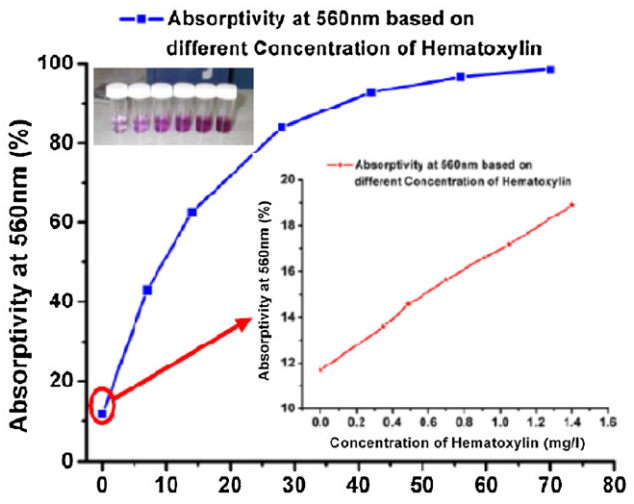

Fig. 8. Results of reference light absorption tests at 560 nm using LAMBDA 750 spectrophotometers.

as a radical initiator (at a concentration of 1 mol% of double bonds), was dropped onto a 700 μm × 700 μm MEMS drug delivery device. The polymerization process was initiated by heating the device up to 60 °C for 5–10 min. MBAA was recrystallized in water before use. Phosphate buffer saline (PBS) solution was prepared from PBS tablets. Scanning electron microscopy (SEM) of the polymerised hydrogel was performed in order to study the surface structure of the resulting polymer (Fig. 6). The images demonstrated that the polymerization occurred successfully and that this polymerization method could indeed be used to directly coat the microchip device with an electro-responsive polymer.

4. Drug delivery experiments

Following the preparation of the PMAA based hydrogel, drug release experiments were performed. A schematic of the electric field responsive controlled drug delivery system is shown in Fig. 7. Hematoxylin was selected as model of a hydrophilic dye. Hematoxylin is a chromophore with a maximum absorbance at 560 nm. Release of the dye from the hydrogel polymer matrix was monitored using UV–visible spectroscopy. The amount of hematoxylin released into the surrounding aqueous media was quantified using a calibration curve established for high and low concentrations of hematoxylin in aqueous solution. Fig. 8 shows reference absorption spectra at 560 nm of the polymer preloaded with hematoxylin dye at high concentrations (0–80 mg/l) and low concentrations (0–1.6 mg/l), measured using a LAMBDA 750 spectrophotometer (PerkinElmer Inc.). A 1 μl volume of the pre-polymerised solution was dropped onto a 700 μm × 700 μm device and polymerised by heating the device at 60 °C for a few minutes. Hematoxylin was loaded into the polymer matrix by allowing the dry hydrogel to swell in the presence of a concentrated Hematoxylin solution in Phosphate buffered saline (PBS) solution at pH 7.3. PBS buffer was selected as a release media in order to mimic biological environments (isotomicity and pH); it is known that PMAA based hydrogels are fully swollen at pH 7.3. Following loading of the hydrogel with dye, the polymer-coated device was immersed in aqueous solution and a 20 V DC voltage was used to trigger dye release from the hydrogel. The release of hematoxylin was monitored over time by taking small aliquots from the release medium. The amount of dye released was quantified according to the reference curve (Fig. 8).

The release profile (Fig. 9) showed that concentration of hematoxylin dye released into the surrounding aqueous solution increased upon application of a voltage to the meander metallic device. The voltage creates a uniform electric field which causes the polymer hydrogel to de-swell, subsequently releasing hematoxylin

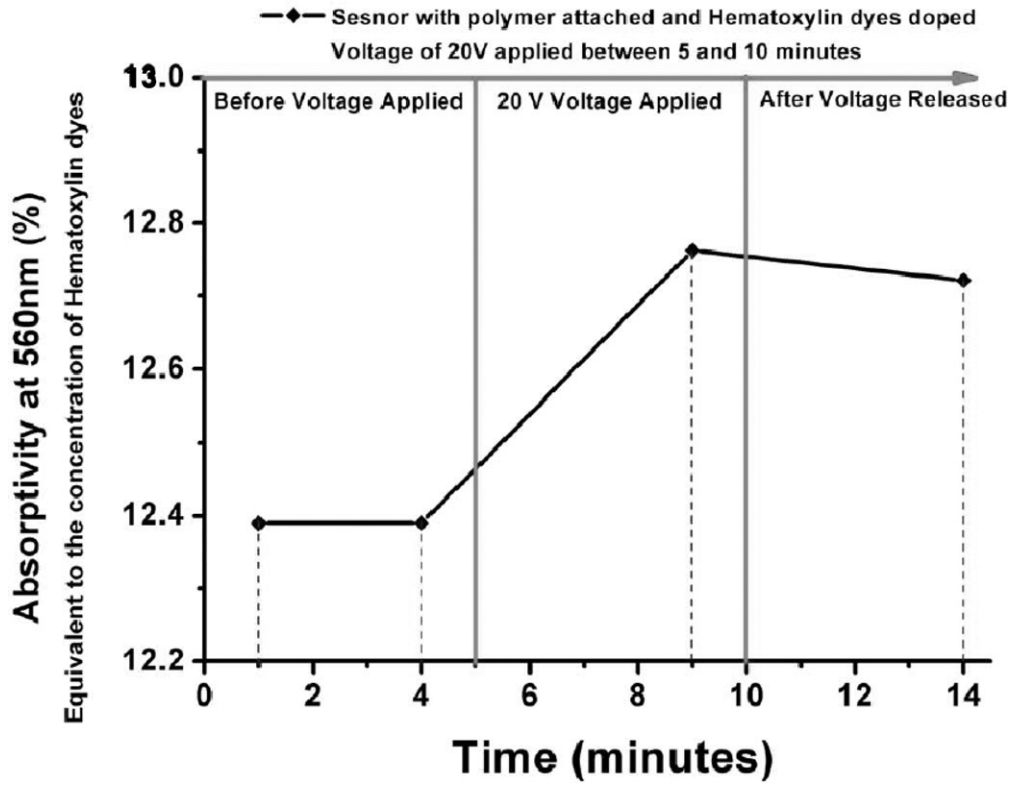

Fig. 9. Hematoxylin dye release versus time in response to applied voltage.

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due into solution. Upon removal of the electrical current stimulus, the release of hematoxylin ceased (Fig. 9). The release profile from the gel matrix clearly is clearly pulsatile. In particular, for anionic polyelectrolytes like PMAA-based hydrogels, an anisotropic deformation of the gel characterised by a contraction at the cathode and a swelling at the anode.

This investigation has successfully demonstrated that Hematoxylin was released from the polymeric matrix as a result of the gel de-swelling upon exposure to an electric field and that hematoxylin release stopped as the gel recovered its initial shape when the electric stimulation was ceased. This result demonstrates that the hydrogels successfully respond to an electric field generated by the fabricated microchip device.

5. Conclusions

A novel MEMS based drug delivery microsystem has been designed and successfully fabricated. The device consists of an array of metallic contacts, able to create to uniform electric field. The electro-sensitivity of a PMAA based hydrogel in combination with the MEMS based microchip is reported here for the first time. The device has the potential for application in 'on-demand' drug delivery systems. A hydrogel polymer matrix loaded with hematoxylin dye, as model of a hydrophilic drug, has been studied. The delivery microsystem operated at normal body temperature (37 °C) under an applied voltage of 20 V. The release rate and dose was accurately controlled. The polymer responds to the electrical stimulus by shrinking and releases the hematoxylin dye into solution. Release of hematoxylin into the surrounding aqueous media was monitored using ultraviolet–visible spectrophotometry at the λ_{max} of the dye (560 nm).

This drug delivery device could be used for the delivery of therapeutic agents for the treatment of chronic illnesses that require multiple dosage regimes. The implantation of such a device in the body, local to the targeted organ could also overcome the issues of systemic drug administration that often lead to toxicity or side effects. The controlled drug delivery system could also improve patient's compliance. Different drug candidates can be encapsulated within the hydrogel polymer matrix. Control of the applied voltage can be used to achieve pulsatile drug delivery. Alternatively, small volumes of the drug may be continuously delivered to maintain the optimum therapeutic dose for the patient.

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Biographies

Dr. **Yufei Liu** is a Knowledge Transfer Officer at the College of Engineering in Swansea University. Dr. Liu was awarded the excellent graduate award from Peking University, China for his B.Sc. in Physics and B.A. in Economics in 2003. Dr. Liu also won the president award from Shanghai Institute of Microsystem and Information Technology, Chinese Academy of Science, China, when he was awarded the M.Eng in Microelectronics and Solid State Electronics in 2006. Dr. Liu was also the research prize winner in the School of Engineering & Physical Sciences, Heriot-Watt University, UK, and was awarded a Ph.D. degree in 2010. He is currently working in multi-disciplinary research and knowledge transfer activities, including micro/nano technology, MEMS and optical MEMS, device simulation and fabrication technologies, material science and surface science, photovoltaics, integrated sensors and lab-on-a-chip technology for point of care applications.

Dr. **A. Servant** received her Ph.D. degree in June 2010 in Materials Chemistry at the School of Biological and Chemical Sciences in Queen Mary University of London, as a Marie Curie Fellow. She is currently working at the University College of London School of Pharmacy, on the development of novel stimuli-responsive nanomaterials with applications for controlled drug delivery in the field of nanomedicine.

Dr. **Owen J. Guy** is Senior Lecturer & RCUK fellow in nanomedicine at the College of Engineering in Swansea University, working in nanotechnology and advanced materials for healthcare applications. Dr. Guy gained a 1st class B.Sc. in Chemistry and the Ayling prize for highest degree in Chemistry at Swansea University in 1997. He was awarded the Leonard Hinkel prize for his Ph.D. (Chemistry) in 2001 for work on the photodegradation of ink-jet dyes in collaboration with Zeneca. His multi-disciplinary research includes nanotechnology, electronic materials, devices & processing technology, surface science, photovoltaics and sensors, funded by EPSRC, EU, Technology Strategy Board and the Welsh Assembly Government. Current projects include: the top ranked EPSRC Grand Challenge in Nanohealth 2009 – developing a micro-needle sampling/drug delivery system and an EPSRC funded project developing graphene biosensors. He is currently an investigator on projects with grant funding of over £4m. OJG has also been a key figure in Swansea's Centre for Nanohealth (CNH), which has just received £21m funding for a new nano-device fabrication facility dedicated to providing nanotechnology solutions for healthcare.

Dr. **Khuloud T. Al-Jamal** received her Ph.D. degree in Drug Delivery from The School of Pharmacy, University of London in 2005. She is now a Lecturer in Nanomedicine at the Institute of Pharmaceutical Sciences at King's College London. Her research interests focuses on designing novel drug delivery systems and their pre-clinical translations into small animal models.

Prof. **P. Rhodri Williams** FInstP FIChemE FLSW FRSA holds a Personal Chair at Swansea University. His research interests include rheology/haemorheology, non-Newtonian Fluid Mechanics and Nanotechnology. His work is supported by the EPSRC (UK), NIHR, NISCHR and industry, on an international basis.

Dr. **Karl M. Hawkins** received his M.Eng in Chemical Engineering in 1998 and his Ph.D. degree in 2002. He is currently a Senior Lecturer and holds a prestigious RCUK fellowship at the Institute of Life Science, College of Medicine, Swansea University. His interests include the development of rheological techniques for the characterisation of the structure and mechanical properties of biopolymer gelling systems. He is the Principal Investigator of an EPSRC first grant award that is developing novel rheological biomarkers of coagulation.

Prof. **K. Kostarelos** received his Ph.D. in Chemical Engineering from Imperial College London and is currently a Chair of Nanomedicine and the Head of the Centre for Drug Delivery Research at The School of Pharmacy, University of London. He is interested in bioengineering novel nanomaterials for the purpose of dug and gene delivery in vitro and in vivo.

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