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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. The meander structured device created a uniform electric field which stimulates drug releases. An electro-active hydrogel based polymer matrix 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 has been stopped. By controlling the voltage and time, 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.

Keywords: Drug delivery; Electric-field responsive; Point of care; Electro-active hydrogel;

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]. To achieve responsive, controllable delivery of active compounds is a major challenge. Two different methodologies have been broadly investigated: drug release payload after a certain time delay or pulsed release in pre-determined sequences [4, 5].

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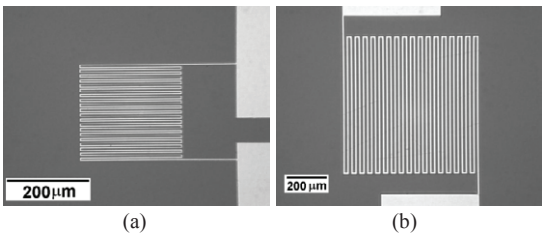
Electro-responsive drug delivery, with microfabricated membrane structures or certain hydrogels, can be used to administer time-legged or pulsed drug release [6-10]. Using hydrogels in three-dimensional high-molecular weight networks, electro-responsive controlled drug delivery, offers prolonged and better control of drug administration, maintaining the drug in the desired therapeutic range with just a single dose, and localized delivery of the drug to a particular organs, which are important in a wide variety of applications in medical and pharmaceutical fields [6-8].

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. Based on an electro-active hydrogel based polymer matrix, the delivery microsystem responds to an electrical stimulus and the shrinking or de-swelling of the polymer matrix enables the encapsulated drug to be released.

2. Device Design and Fabrication

Metallic meander tracks were designed in widths of 3μm and 10μm. The fabricated devices, shown in Fig. 1, have footprints of 240μm×250μm and 700μm×700μm, respectively. The 100nm thick metallic contacts were produced by sputtering titanium/platinum metallic contact layers, and patterned using an ion beam etching process. An annealing process for 5 hours at 350°C was performed to have reliable functional devices, which helped to secure the electrical characteristics of the deposited and patterned metallic meander tracks. Both thermal and electric field properties of the device have been simulated using finite element methods. The simulation result in Fig. 2 (a) shows that a uniform electric potential was created along the metallic meander tracks, which resulted in a uniform electric field along the meander metallic contacts (except the end corners) shown in Fig. 2 (b). In simulations, a voltage of 1.67V was applied to 3-unit of meander metallic contact structure equivalent to 20V on the actual fabricated structure of 36 meander units (Fig. 1(b)). The thermal properties of the meander structures under a constant DC bias have been measured using a probe station coupled to a HP 4142b electrical analyzer (Fig. 3) assisted with a thermal couple meter. The device temperatures under different DC conditions are shown in Fig 4. These results show that fabricated devices operate at normal body temperature (37°C) when a DC bias of 20V is applied to the meander structured device.



(a) (b)

Fig. 1. Fabricated drug delivery devices with meander metallic structures in track width of (a) 3μm, and (b) 10μm.

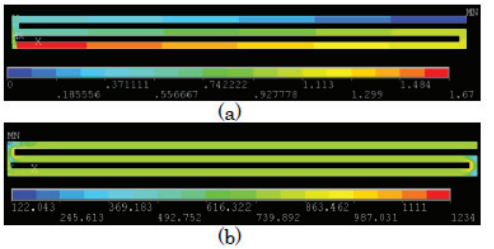


Fig 2. FEM simulation results of (a) electric potential and (b) electric field vector summation in a 3-unit metallic meander structure.

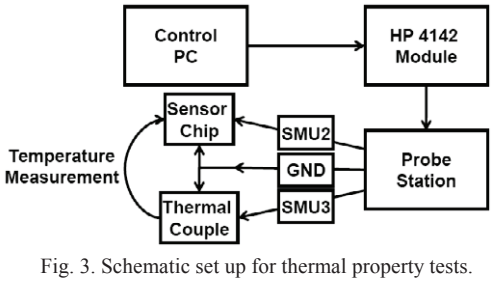


Fig. 3. Schematic set up for thermal property tests.

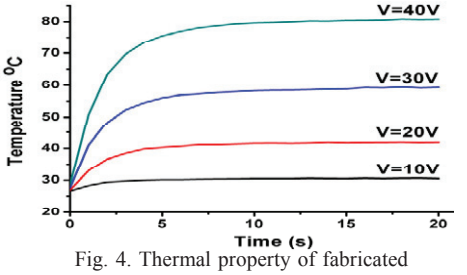


Fig. 4. Thermal property of fabricated devices under different DC voltages.

3. Drug Delivery Experiments

A schematic of the electric field responsive controlled drug delivery is shown in Fig. 5. Hematoxylin was selected as model of hydrophilic drug. Hematoxylin is a chromophore with a maximum absorbance at 560nm, therefore release from the hydrogel polymer matrix can be easily monitored using UV-visible spectroscopy. The amount of hematoxylin released in the media can be quantified using the calibration curve established at high and low concentrations. Shown in Fig. 6, reference absorption spectra at 560nm of the polymer preloaded dye in deionized water at high concentrations (0 to 80mg/l) and low concentrations (0 to 1.6mg/l) were pre-measured using a LAMBDA 750 spectrophotometer (PerkinElmer Inc.). A 1μl volume of the pre-polymerised solution, containing methacrylic acid as monomer, N,N'-methylene bisacrylamide as cross-linker and potassium persulfate as initiator, was dropped onto a 700μm×700μm device and polymerized by heating the device up to 60°C for a few minutes. Hematoxylin was loaded into the polymer matrix by swelling of the dry hydrogel. This was performed by immersing the device in hematoxylin solution at high concentration for 30 minutes. A 20V DC voltage was used to trigger drug release from the hydrogel. The release of hematoxylin was monitored by taking 3ml aliquots from the media each time while the voltage was applied on and off. The release profile (Fig. 7) show that concentration of hematoxylin dye in the solution increased upon exposure to the uniform electric field created by the meander metallic stimulating dye release into the solution. The amount of dye released from the polymer matrix was quantified according to the reference curve (Fig. 6). When the applied voltage was stopped, the released of hematoxylin was significantly reduced, leading to a pulsatile hematoxylin release profile. Alternatively, small volumes of the drug may be continuously delivered to maintain the optimum therapeutic dose for the patient in conjunction with a diagnostic device.

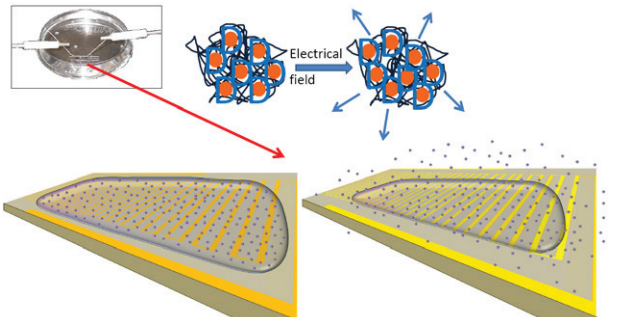


Fig. 5. Schematic of polymer de-swelling drug delivery device due to electronic field.

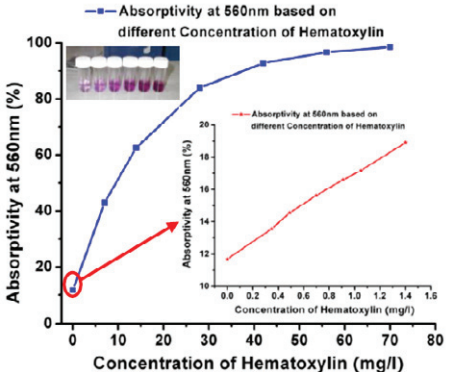


Fig. 6. Results of reference light absorption tests at 560nm using LAMBDA 750 spectrophotometers.

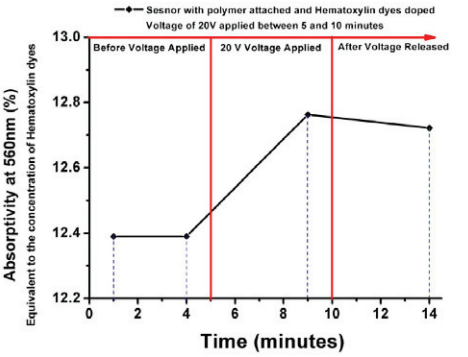


Fig. 7. Hematoxylin dye release VS time in response to applied voltage.

4. 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. A hydrogel polymer matrix loaded with hematoxylin dye as model of 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 in the media was monitored using ultraviolet-visible spectrophotometry at the λ_{max} of the dye (560nm).

Different drug candidates can be encapsulated within the hydrogel polymer matrix. The de-swelling of the polymer upon exposure to the applied electric field enables the encapsulated drug to be released from the 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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