Engineering Implantable Microfluidic Drug Delivery Device for Individualized Cancer Chemotherapy

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Abstract: Cancer patients nowadays suffer from serious side effects and unpleasant experiences when treated with anti-cancer drugs. Conventional drug delivery methods including drug pills/capsules, topical drug gels/drops and drug injections are too simple, incapable of providing controllable and efficient tumour drug delivery in cancer treatment. Implantable drug delivery devices open a new horizon for drug treatment. Through device implantation locally onto disease site, high efficiency drug delivery can be achieved. Utilizing techniques from microfluidics, precise manipulation of drug fluids by these devices offer great advances for treatment. In our study, an electrochemical actuated microfluidic drug delivery device was fabricated and studied *in vitro* and *in vivo*. Cultured pancreatic cancer cell colonies were successfully inhibited by programmable Doxorubicin treatments controlled by devices. Further, 12 devices were implanted into 12 Kunming mice for evaluation of biocompatibility and drug delivery performance. Tissue biopsy and blood sample analyses indicated all 12 mice remaining healthy after devices implantation. Adrenaline was delivered to the abdominal cavity of the mice by using the implanted device and compared with conventional injection as a positive control. Both approaches have shown that they are able to precisely control and manipulate the increment rate of blood pressure in the small animals.

1 INTRODUCTION

Chemotherapy is an important method in treating cancer. However, nowadays cancer patients suffer from serious side effects and unpleasant treatment experiences during chemotherapy with anti-cancer drugs, which are usually highly toxic in order to inhibit the rapid growth of cancer tumors (Song et al., 2013, Song et al., 2014, Gensler et al., 2010b). Conventional drug delivery methods including drug pills/capsules, topical drug gels/drops and drug injections have either low efficiency, wasting most of the drug formulation during transportation via systemic circulation, or invasive; which causes pain and cellular damage (Li et al., 2010, Li et al., 2009, Li et al., 2008, Tsai and Sue, 2007). Also only simple drug profiles can be achieved by conventional methods (Elman and Upadhyay, 2010). The application of conventional drug delivery methods has reached its limit in terms of controllability and efficiency for chemotherapeutic treatment of tumours. Recent developments in drug delivery devices enable drug carrying devices to be implanted locally at disease sites, providing an unprecedented efficiency in drug delivery (Gensler et al., 2012, Meng and Hoang, 2012, Saati et al., 2010b, Song et al., 2013, Farra et al., 2012). Leveraging on microfluidic technologies, precise manipulation of drug fluids by these devices offer great advances in treatment. These devices present enormous capabilities; allowing the tailoring of drug dosages, drug delivery profiles, as well as localized and targeted delivery of drugs to the disease sites. Through the optimization of these parameters, effective treatment fitting the needs of every individual patient can be realized. This approach will minimize the side effects of drugs formulation to the body while maintaining the desired therapeutic concentration for effective therapy of illnesses.

Currently, there is one type of implantable drug delivery devices that has a chip-like structure, consisting of an array of micro-reservoirs (10 – 200nL capacity). By selectively open those micro-reservoirs, designed drug formulations will diffuse to disease site. These devices have been tested *in vitro* (Chen et al., 2009, Chung et al., 2009, Elman et al., 2009, Yang et al., 2011), *in vivo* (LaVan et al.,

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2003, Prescott et al., 2006) and in human(Farra et al., 2012). However, these drug delivery microchips are unsuitable for cancer chemotherapies due to their limited reservoir volume, necessitating periodic re-implantations to achieve the long term drug treatment effects (Santini Jr et al., 2000). New studies proposed to solve this challenge by employing an implantable drug delivery device with a single reservoir system instead of relying on multiple micro-reservoirs. The device system is integrated with a MEMS micropump actuator for driving the fluid out from the large reservoir (Tsai and Sue, 2007). The localized delivery of drugs is then achieved by using a cannula connected to the drug reservoir and thereby allowing the drugs to be delivered to the targeted tumor site. It is demonstrated that these devices can be implanted subcutaneously (Shobo et al., 2011) thereby allowing one to easily refill the system with drugs using a specialized port or via a syringe (Po-Ying et al., 2010, Tng et al., 2013). For cancer treatment, the significance of refilling serves not only to extend the drug therapy period, but more importantly, the capability to amend the formulations used, especially when drug resistance is encountered (Song et al., 2013, Gottesman, 2002). Single reservoir drug delivery devices have been extensively tested for *in vitro* (Gensler et al., 2012, Shobo et al., 2011, Gensler et al., 2010b, Lo et al., 2009b), ex-vivo(Li et al., 2008) and *in vivo* (Saati et al., 2010a, Gensler et al., 2010a, Ambati et al., 2000).

Here, we demonstrate an electrochemically actuated, single reservoir implantable microfluidic drug delivery device for cancer treatment studies. Fabrication was achieved using MEMS microfabrication techniques with biocompatible materials. The use of the microfluidic drug delivery device for cancer chemotherapy *in vitro* is presented and the experimental results highlights the drug delivery device's capability of customizing specific drug delivery profiles for treating different types of pancreatic cancer cell lines. Furthermore, working towards usage in clinical settings, the impact and biocompatibility of these devices implanted in the body were carefully studied *in vivo*. We carefully examine the impacts and biocompatibility of the implantable microfluidic drug delivery device by subcutaneously implanting them into 12 Kunming mice for a 28 days observation. In addition, we also demonstrate the device can be successfully used for drug delivery therapy under implantation settings upon comparing its effectiveness with the conventional intravenous injection method.

2 DESIGN

The microfluidic drug delivery device is constructed by three parts: the Polydimethylsiloxane (PDMS) drug reservoir, the Polyolefin cannula and the metal electrode actuator (Figure 1). PDMS and Polyolefin were chosen as construction materials for their proven bio-compatibility. PDMS has an attractive resealing feature thus the singular drug reservoir constructed of PDMS can be filled/refilled using syringe and needle without damage its structure(Lo et al., 2009a). The metal electrode actuator contains a pair of interdigitated Pt/Ti fingers as anode and cathode. When supplying bias voltage on the electrodes, Hydrogen (H_2) and oxygen (O_2) gases were generated by water electrolysis. The formation of the gases quickly increases the pressure within the drug reservoir, and then pushes drug solution within the reservoir to be released through the long cannula, reaching to the disease site. This single reservoir together with long cannula design negates the requirement to implant the entire device at the disease site. This is a major advantage as diseases are hard to be reached by implantable chips due to spatial and physiological constraints at the disease site can now be treated with implantable devices. For example, Ambati et al. have reported the subcutaneous implantation of an osmotic pump between the scapulars with a long cannula delivering drug into the choroid and retina of rabbit eye, where it was hard to implant an entire drug delivery chip (Ambati et al., 2000).

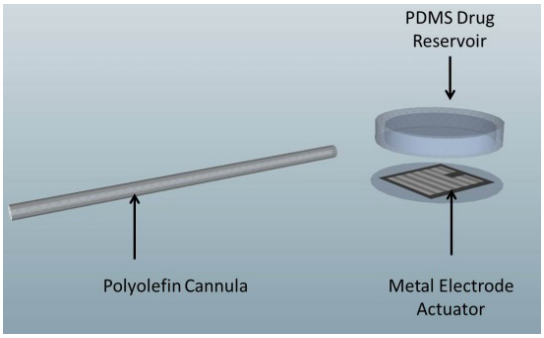

Figure 1: Design of the microfluidic drug delivery device.

In the traditional design of metal electrodes, a 2-layer electrode design was used (Song et al., 2013, Li et al., 2008). Titanium served as adhesive layers for platinum/gold onto substrate, which resists oxidation in the electrolysis reaction. However, metal electrode structure delamination was frequently observed when the actuator was designed to be miniaturized for implantation into small

animals. And the delamination would negatively affect the actuation performance as well as lifetime (Hang Tng et al., 2014). Facing this challenge, we invented a nanosandwiched Pt/Ti multi-layer electrode design. The multilayered design of the electrode was constructed with several repeating units of thin Ti/Pt layers instead of one. All unites are bonded together to withstand forces from water electrochemical reaction. A relatively thick layer of Ti at the top of metal structure provides additional protection for the electrode (Figure 2). In our study, the new metal electrode actuator design has shown to enhance the lifetime up to 400% more than conventional, despite its smaller feature size (< 20μm) than before.

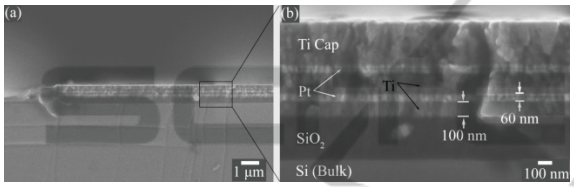

Figure 2: Cross section SEM images of nanosandwiched multilayer electrodes (a) An overview of a metal electrode. (b) An enlarged electrode marked by measurements. Images are reprinted with permission from Royal Society of Chemistry (RSC).

3 FABRICATION

Nanosandwiched Pt/Ti multi-layer electrode actuator was fabricated through photolithography, electron beam metal evaporation and lift off processes. AZ5214 photoresist was spun coated onto the Si substrate at 4000 rpm for 45 s followed by a pre-exposure bake (105 ˚C, 2 min). The electrode pattern was generated by photolithography. Five metal layers of titanium and platinum were then deposited respectively (Ti-Pt-Ti-Pt-Ti) by electron beam evaporation to create the nanosandwich structure. The wafer was rinsed with acetone to lift-off the remaining AZ photoresist and release electrodes. Two thin copper wires were bonded to electrodes with silver conductive adhesive paint. The Pt/Ti multilayer electrode actuator measures 5mm long, 5mm wide and 0.5mm thick. The actuator was integrated as the base of the drug reservoir.

Drug reservoir was fabricated through soft-lithography processes. SU-8 photoresist was spun coated onto the Si substrate at 1000 rpm for 60 s followed by a pre-exposure bake (110 ˚C, 4 hour). Device mold pattern was generated by exposure (420 W, 90 s, hard contact). A post exposure bake (95 ˚C, 1 hour) and developing was performed to release the SU-8 mold. Polydimethylsiloxane (PDMS) was poured into the SU-8 mold and then degassed with in a vacuum oven. The PDMS was then cured at 120 °C for 20 min and was subsequently removed from the mold to get drug reservoir pattern. Electrode actuator and drug reservoir were assembled using PDMS. The PDMS drug reservoir measures 10mm long, 10mm wide and 2mm thick. A polyolefin cannula measuring 30 mm long and 0.5mm inner diameter and 0.8mm outer diameter was then bonded to drug reservoir using PDMS. Subsequently, the whole device was baked at 120 ˚C for curing.

4 RESULT AND DISCUSSION

4.1 Device Characterization

The delivery performance of our electrochemical actuated microfluidic drug delivery device was studied. Drug flow rates versus supplied voltages were measured. Characterization results are shown in figure 3.

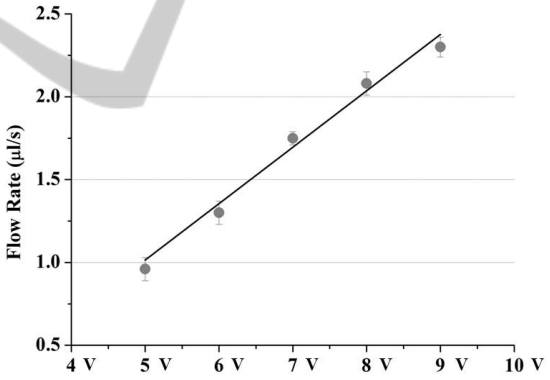

Figure 3: Characterization of drug delivery flow rates at 5, 6, 7, 8 and 9 V (n = 4, mean ± *SD*).

The result showed that flow rates from 1 μl/s to 2.3 μl/s can be achieved with supplied voltage from 5 V to 9 V. An approximately linear trend was observed. The controllability of actuator on delivery drug flow rates offers great advances in treatment, providing flexible treatment profiles (flow rates, drug volume and treatment timing) on demands. By using the reliable nanosanwiched metal electrode actuator, devices showed great reliability and consistency during drug delivery as shown by the relatively small standard deviation. No fluid leakage occurred during the whole test. It is worth to mention that long-time operation of electrolysis actuation with high voltage may lead to temperature

rising. In the characterization of our devices, no significant raise in temperature occurred during a reasonable operation time.

4.2 Individualized Cancer Treatment Study *in Vitro*

Experiment setting is shown in figure 4a. Two types of pancreatic cancer cell (MiaPaCa-2 and Panc-1) were cultured in petri dish for 10 days until they have grown into colonies (Figure 4b). Cancer chemotherapy drug doxorubicin (Dox) was delivered to cultured cancer cell colonies using our microfluidic drug delivery device automatically for 8 days. Gaining from the device's controllability on drug delivery profiles, two customized drug dose profiles (program I: 6μg of doxorubicin delivery in day 0, day 1 and day 2, program II: 9μg of doxorubicin delivery in day 0 and day 3) were conducted onto the two types of pancreatic cancer cells. The cancer cell colonies size changes were monitored during the 8 days treatment. Our results have shown that cancer colonies lost their viability after chemotherapy (Figure 4c) and the growth of cancer cell colonies was successfully inhibited as compared with control group (Figure 5). It is important to notice that, the MiaPaCa-2 group and Panc-1 group have demonstrated different response under each customized treatment profile. Under the treatment profile "program II", the treatment effects occurred at DAY 3 when the drug concentration reached 18μg for both MiaPaCa-2 and Panc-1. However, under the treatment profile "program I", the timing when inhibition of growth occurred was different in each group (DAY 1 and DAY 2), which means 12μg of DOX delivery would be sufficient to inhibit MiaPaCa-2 pancreatic cancer. Thus treatment profile "program II" may not be suitable for treating MiaPaCa-2 cancer for possibly overdosing the drug amount. Therefore, using the implantable device for an controlled drug delivery treatment, it is possible for designing and conducting individualized treatment profiles to treat and cure cancers towards each patient's needs, in the meanwhile to avoid side effects of chemotherapies.

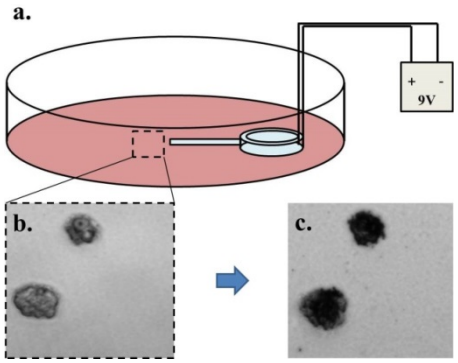

Figure 4: Pancreatic cancer chemotherapy using microfluidic drug delivery device *in vitro*: a. Drug delivery device is placed in cell culture dish powered with a 9 volt battery. b. Microscopy image of pancreatic cancer cell colonies after 10 days culturing. c. Cancer cell colonies after chemotherapy.

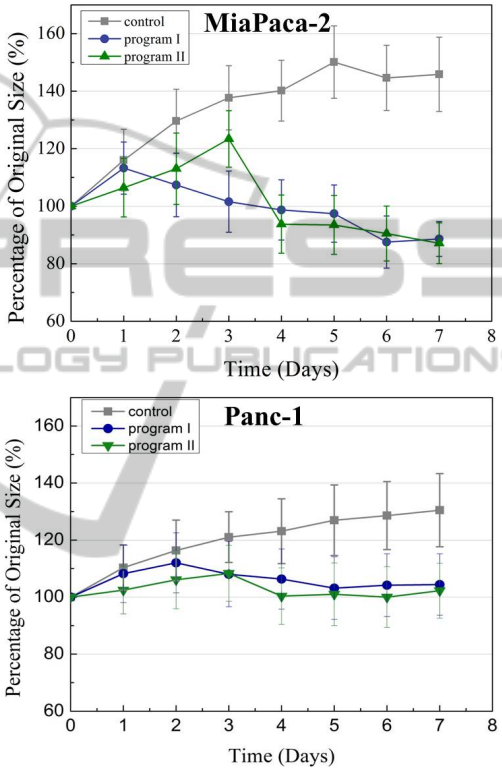

Figure 5: Pancreatic cancer cell colonies size changes under programmed treatment profiles. Pictures are reprinted with permission from Royal Society of Chemistry. Images are reprinted with permission from Royal Society of Chemistry (RSC).

4.3 Device Implantation *in Vivo* Study with Kunming Mice

In Vivo study has been conducted for evaluating the biocompatibility and overall performance of our microfluidic drug delivery device. In total 12 devices were implanted subcutaneously in 12 Kunming mice where the long cannula was inserted into the animal abdominal cavity for drug delivery purpose. The microfluidic drug delivery device can be easily implanted through minimally invasive surgery procedures by creating 2 separate small incisions in the small animal (Figure 6a, b). All 12

mice remained alive and healthy after surgery throughout the 28 days experiment. 9 mice carrying devices were involved into biocompatibility test and other 3 mice were in implanted drug delivery study. Figure 6c shows the representation of a device implanted in a mouse. From the basic observations, we concluded that the device implantation did not cause major adverse impacts to the implanted mice.

Furthermore we carefully examined the biocompatibility of our device by blood analysis and tissue histology. At DAY 2, DAY 4 and DAY 28, 3 mice were sacrificed and their 1 ml blood samples as well as tissues samples surrounding implanted devices were acquired. Blood markers including haemoglobin (Hb), total bilirubin (TBILI), direct bilirubin (DBILI), red blood cell (RBC) count, neutrophils (NE), monocytes (MO), lymphocytes (LY), and white blood cell (WBC) showed no abnormal variance indicating no severe infection and adverse immune response generated from the implantation for 28 days. Alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine (CRE), and uric acid (UA) level indicated the healthy liver and kidney functions of tested mice.

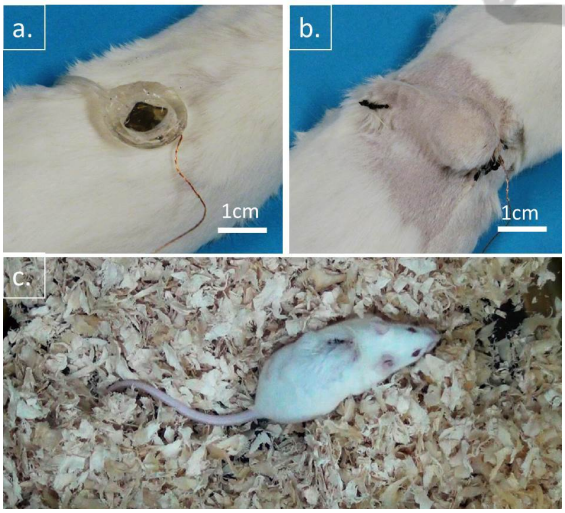

Figure 6: Device implanting into Kunming mice: a. Before implantation. b. After implantation. c. Photography of Kunming mouse 10 days after device implantation.

Surrounding tissue samples showed a normal wound healing process on tested mice from DAY 2 to DAY 28 (Figure 7a, b). Implanted devices were fully encapsulated by fibrous tissues at DAY 28 (Figure 7b). Further we have done microscopy of haematoxylin-eosin (H&E) stained paraffin-embedded fixed tissue sections. The observations showed that, in DAY 4 (Figure 7c), a slight inflammation and edema occurred at device implantation area, but in DAY 28 (Figure 7d) surrounding tissues returned to normal with newly capillaries and fibrous cells formed. The results strongly suggested that there is no rejection of the implanted devices showing in tested animals. Our microfluidic drug delivery device presented great biocompatibility during the implantation with Kunming mice.

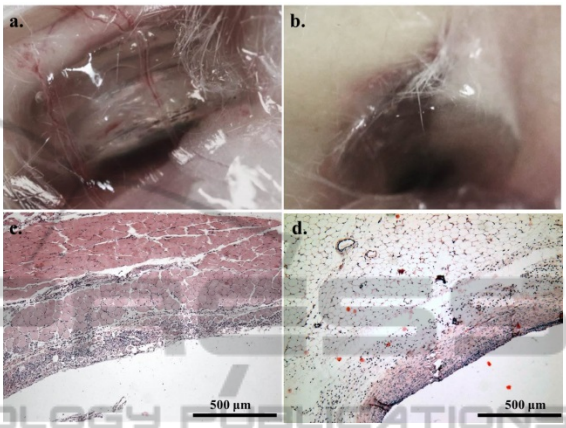

Figure 7: Biocompatibility studies of microfluidic drug delivery device implantation: a. Photography of device 2 days after implantation surgery. b. Photography of device 28 days after implantation surgery. c. Microscope photos of subcutaneous tissue surrounding implanted device, haematoxylin-eosin (H&E) stain, day4 with 10X magnification. d. H&E stained tissue sample, photo taken at Day28 with 10X magnification.

4.4 Implanted Drug Delivery

3 microfluidic drug delivery devices carrying 50 µl of adrenaline were implanted into 3 Kunming Mice. After implantation, devices were switched on for 25 seconds to deliver the adrenaline formulation into abdominal cavities of mice. The changes of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before/5-minute after adrenaline delivery. As comparison, 50 µl adrenaline formulations were intraperitoneal injected to 3 Kunming mice without implant as control group. The result showed that the SBP and DBP of both control and experimental groups increased as the same trend after drug delivery (Figure 8a, b). We concluded that the microfluidic drug delivery device is functioning properly under the implantation setting. As the adrenaline formulation worked similarly in both groups, we assume that in the application of microfluidic drug delivery device for cancer treatment, chemotherapy drug activity would not be affected by the new delivery method.

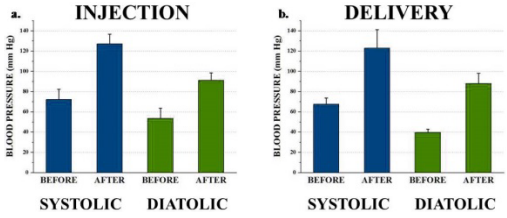

Figure 8: Blood pressure measurement data: a. Drug delivery by syringe injection. b. Drug delivery by devices. Both SBP and DBP were measured for every mouse.

5 CONCLUSIONS

Implantable microfluidic drug delivery devices have been shown to have great potentials in futuristic cancer treatment. Their controllability and ability to leverage on the strengths of anti-cancer drugs has made them an attractive option for overcoming the present challenges faced in medicine. Demonstrated with the *in vitro* pancreatic cancer model, we concluded that through the programing of these devices, chemotherapy could potentially be individualized for every individual to gain better treatment effects. The biocompatibility and drug delivery performance of the device were demonstrated with Kunming mice model *in vivo.* Future researches on the microfluidic drug delivery device will be focused on treatment effects of different cancer tumor models on small animals, and further clinical trials.

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