On-Demand Drug Release Device: An Electrophoretic Approach

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ABSTRACT

In this research, we present an electrically stimulated membrane-based drug delivery device to release drugs on demand. Hydrogels with ionic model drugs were sealed in a cylindrical reservoir with a separation membrane. An electric field was generated across the drug container and ionic drug molecules were expelled from the hydrogels into bulk solution in vitro. Drug release rates were found to be proportional to the applied electric field strength. Pulsatile drug release in response to alternating the electric field was achieved with an on/off ratio up to 10. The release rate can further be controlled by programming voltage waveform to deliver ionic drugs on demand.

KEYWORDS: Programmable drug delivery, Electric stimulus, Pulsatile drug delivery systems.

INTRODUCTION

Recent development in drug release devices has shown its capability in delivering accurate amounts of drug at specific location. Various types of drug release devices, such as hydrogel[1], nano-particles[2], and membrane-based reservoir devices[3], have been extensively studied in the literature. Among many drug delivery devices, pulsatile drug delivery systems (PDDS) have drawn attention recently because PDDS allows repeatable and reliable drug release flux for clinical needs. In this research, an electrically driven drug release device is developed based on electrophoretic nature of drug molecules. Hydrogels containing ionic drugs were sealed in a cylindrical reservoir of 45 μL with a separation membrane. Two screen-printed carbon-paste electrodes parallel to the reservoir are used to develop an electric field inside the drug container. A model ionic drug, methylene blue, was used to demonstrate the capability of this device. With a constant DC applied voltage, the ionic drug molecules from the device with the help of an external electric field. The release rates from the device are proportional to applied voltages, and can be controlled within an order of magnitude. By programing the voltage waveforms, pulsatile drug release can also be achieved with an on/off ratio up to 10.

EXPERIMENT

The electro-stimulated membrane-based drug delivery device is composed of a top electrode, separation membrane, drug reservoir, and a bottom electrode (Fig.1a). First, a hollow drug reservoir was made by compressing hot ethylene vinyl acetate (EVA) melt on an aluminum mask. The main body of the reservoir is a cylinder of 3 mm in diameter and 1.5 mm in height. Above the cylinder, a small pin hole of 500 um in diameter was used as a drug release channel. A piece of PTFE membrane was gently put right above the pin hole and bonded to the reservoir thermally. Then, a top electrode was screen-printed on the EVA reservoir surface with carbon paste. Next, 45 μL of drug-containing gel was loaded in the reservoir with a pipette. An EVA slab with screen-printed bottom electrode was sealed under the reservoir with EVA melt in order to prevent leakage. Electric wires were used to connect the electrodes with a DC voltage source for drug release test. Finally, we demonstrate the performance of the drug delivery device (Fig.1b).

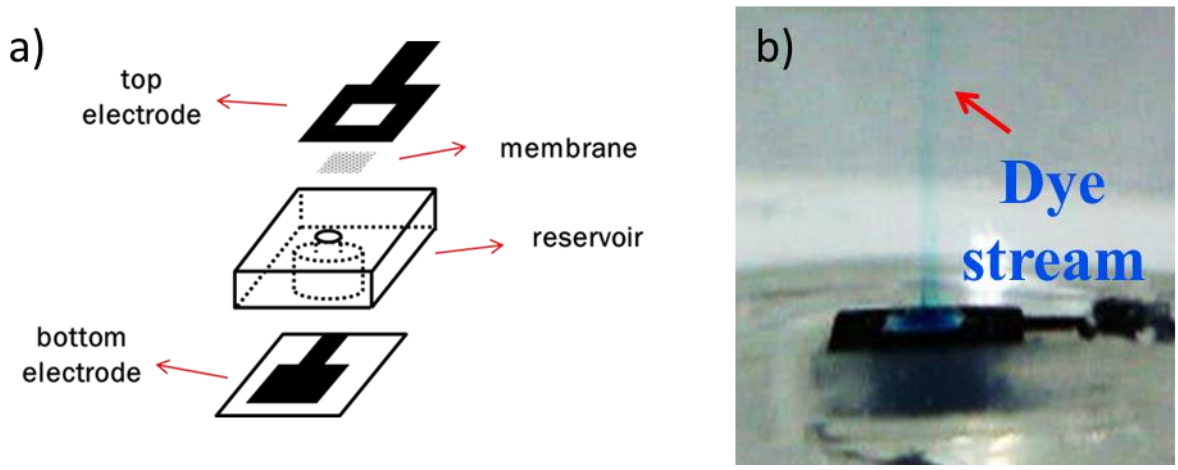

Figure 1：a) The schematic diagram for the electrically stimulated membrane-based drug delivery device. b) A submerged device containing methylene blue in PBS solutions with an applied voltage of 7 V.

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RESULTS AND DISCUSSIONS

Fig. 2 shows an example of pulsatile release of MB by modulating applied voltage waveforms. Initially, to reduce the diffusional drug release, a negative bias voltage was applied on the bottom electrode to hold the positively charged MB molecules. In the bulk solution, nearly no MB was detected within the first 20 minutes, and the color of the separation membrane remained unchanged (white). At t=20 minutes, the applied voltage at the bottom electrode was switched to +3.5V, and MB started to release quickly. Within 10 minutes, one can observe a blue spot on the separation membrane, indicating the permeation of MB through the membrane. MB was then detected in the bulk solution from UV spectra. After 20 minutes of applying +3.5V voltage, the release rate reached a plateau and was kept constant in the next 20 minutes. To shut off the drug release, the voltage at the bottom plate was switched to -3.5 V again at t=59 minutes. The release rate dropped down quickly to a low level within 5 minutes but with a small release rate possibly due to the diffusion of residual MB in the membrane. The response in drug release rates to electrical stimuli is so fast that the absorbance profile presents nearly like a square wave as that of applied voltage. Thus, the applied voltage waveform can be further modulated to program the drug release rates.

The drug release rate can be further modulated by programming the voltage waveforms. A square wave sequence with a fixed amplitude was used to test the device performance on sequentially pulsatile drug release Fig.3. Each pulse cycle contains two modes: the device releases MB at the "on" state by applying a positive voltage at the bottom electrode. The drug molecules are expelled by the bottom electrode and move toward the bulk solution, and hence release large amount of drugs. In the opposite, the device will be at the "off" state at a negative applied voltage. The data show when the applied voltage is 3.5 V, the difference in release rates between on and off states with an on/off ratio of 10.

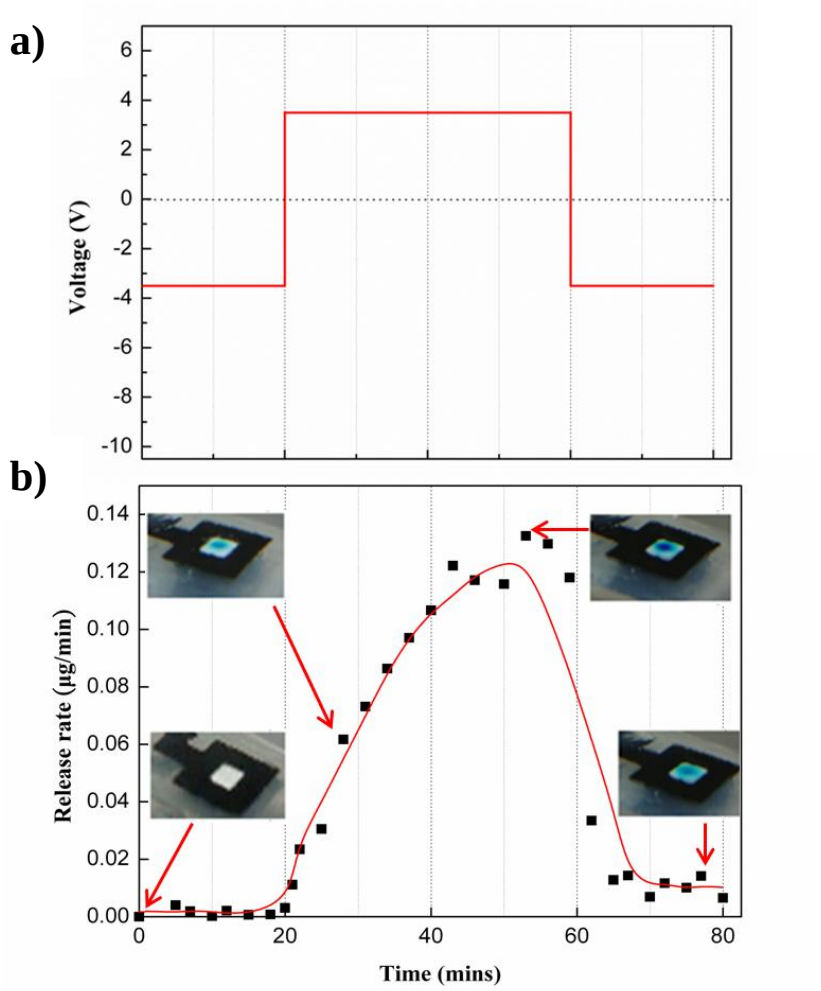

Figure 2：On/off trigger test for pulsatile drug delivery. (a) The applied voltage waveform for pulsatile drug release. (b) The response in absorbance of bulk solution at 663 nm. The inset pictures show the color transition of the separation membrane at different times as pointed by the arrows.

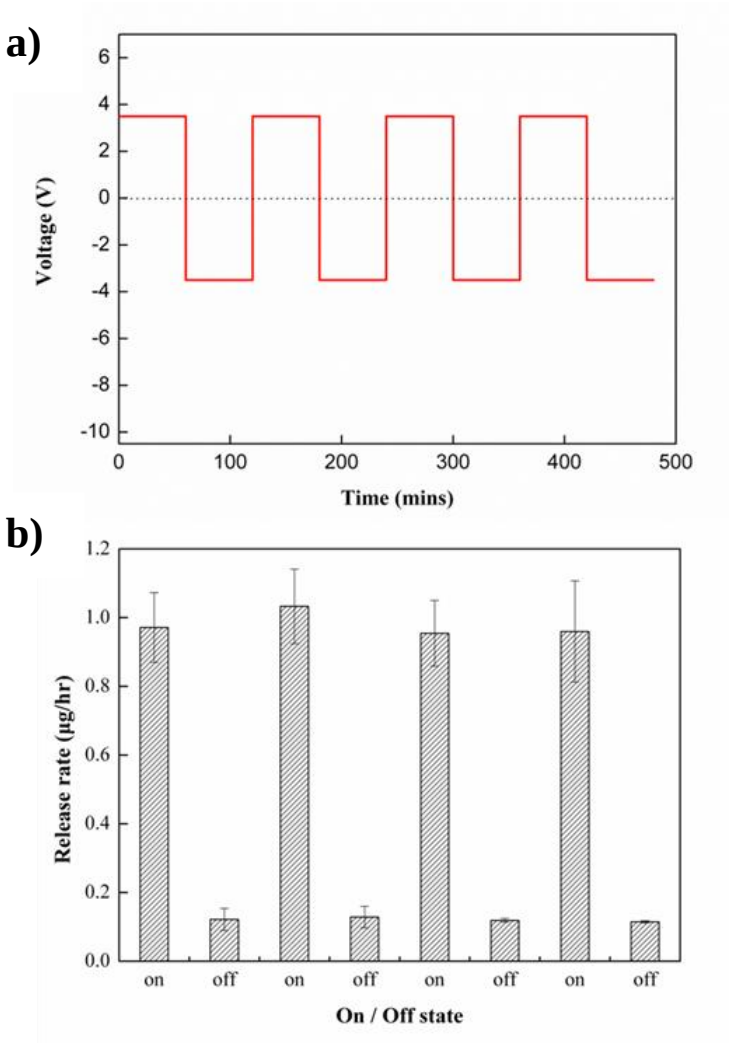

Figure 3：(a) The waveform for sequential pulsatile drug release: each on/off cycle contains a positive voltage to turn on the pulsatile release and a negative voltage to turn off the release rate. (b) Release rates of MB over four successive on/off cycles at various applied voltages.

Conclusions

In this research, an electrically driven drug delivery device is fabricated to actively eject ionic drugs multiple times from a membrane-sealed reservoir of 45μL into surrounding fluids. Methylene blue (MB), a cationic drug, was used as a model drug to test the capability of the fabricated device. This drug delivery device shows the feasibility of applying electrophoretic approach to deliver ionic drugs. By applying specific electric waveforms, one can control not only the drug release rates but also the timing of drug release. Same approach can be further extended to other ionic drugs, such as insulin, micelles, vesicles, and surface charged nanoparticles for the realization of drug release on demand.

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