Simple minimally-invasive automatic antidote delivery device (A2D2) towards closed-loop reversal of opioid overdose

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ABSTRACT

With approximately 48,000 attributed deaths in 2017, the opioid overdose is now the leading cause of death amongst Americans under the age of 50. The overdose process can be interrupted by the administration of naloxone, a safe and effective opiate antagonist that can reverse the effects of overdose and minimizing the delay in administering the antidote is critical in preventing permanent damage to patients. A closed-loop implantable drug delivery system is an ideal solution to minimize the response time, however, they often feature complex designs that are expensive to fabricate and require a more invasive surgical implantation. Here we propose a simple, low-cost, minimally-invasive automatic antidote delivery device (A2D2) that can administer a large dose of naloxone upon detection of overdose-induced respiratory failure. The subcutaneously placed device can be activated using an externally applied time varying magnetic field from a wearable device. Using a custom magnetic field generator, we were able to release the drug within 10 s. Our bench-top evaluation showed that A2D2 can release 1.9 mg of powdered drug within 60 s and up to 8.8 mg in 600 s. We also performed in vivo evaluation to demonstrate rapid drug releasing capability in the subcutaneous space of mice. However, we saw a small amount of leakage (1.75% of payload) over the course of 1000 h of simulated implantation. Thus, additional research is needed to verify the long term stability of our device and to demonstrate the closed-loop release mechanism to revive overdosed animals. Nevertheless, our preliminary results show the potential of using a simple, low-cost, subcutaneous device for emergency drug delivery application.

1. Introduction

In 2017, the amount of opioid-related deaths in the United States grew to 48,000, making the opioid overdose the leading cause of mortality amongst Americans under the age of 50 [1]. Opiates are widely used as pain medication because their receptors are found in parts of the central nervous system that regulate pain perception [2]. However, opioid receptors are also found in the brainstem and other areas of the brain that control respiration [3,4]. As such, binding of opiate to these receptors can not only alleviate pain but it can also cause severe respiratory depression and death [5–7].

Naloxone is an opiate antagonist that can reverse the effects of

natural, semisynthetic, and synthetic opioids [5]. To curtail the increasing trend of opioid overdose-related mortality, naloxone is widely available in many states as a harm reduction strategy [8]. Although naloxone can be administered either via an injection (Evzio®, 0.4–2 mg) or as a nasal spray (Narcan®, 4 mg), the most common route used for naloxone delivery is via subcutaneous or intramuscular injection [9,10].

To ensure effective reversal of opioid overdose, it is critical to deliver naloxone as quickly as possible [11]. However, many opioid users are often found alone and incapacitated at the time of overdose to self-administer the life-saving antidote. Our hypothesis is that an automatic closed-loop naloxone delivery system may prolong the time necessary

for patients to obtain appropriate medical attention thereby reducing the overall opioid-related mortality. However, existing implantable devices are often expensive to fabricate with complex designs and limited payload for large-scale utility.

Here we present a low-cost, single-use, minimally-invasive automatic antidote delivery device (A2D2) that can administer a large dose of naloxone at the time of overdose. The idea of implantable drug delivery system (DDS) goes back to 1979 [12,13]. Although there are many examples of implantable DDS for various applications including pain management [14], cardiac resuscitation [15], osteoporosis [16], cancer [17], schizophrenia [18], and birth control [19], we found no reports of implantable devices for combating opioid overdose. For overdose-responsive drug delivery, a burst release is desirable rather than a continuous infusion method found in many pain management and cancer therapy. Many of these existing systems feature integrated power supply, which requires a robust device packaging and a more invasive implantation procedure. Micro-electro-mechanical systems (MEMS) technologies are often used to fabricate intricate structures that can fine-tune drug delivery in terms of payload, speed, and timing [20–22]. However, conventional MEMS technology often uses layer-by-layer fabrication which may cause premature device failures such as delamination [23]. Furthermore, the microscale devices often require expensive packaging processes. Therefore, a simple and manufacturable design for DDS is ideal for reliable long-term operation in situ.

In this work, we demonstrate a simple high-density polyethylene (HDPE)-based naloxone delivery capsule that costs less than $0.50 to fabricate. The minimally-invasive device features a single payload of up to 12 mg of powder or 20 μL of liquid forms of naloxone ($1–5 in drug cost). The miniature device is small enough to be placed percutaneously via a trocar or a biopsy needle in an outpatient setting. The device features a phase change material (PCM) that can switch between solid and liquid phases as it absorbs or releases heat. Therefore, PCM can be used as a simple thermally-actuated valve (i.e., solid-to-liquid) to release drug payload from a capsule on demand. The simple device features a stainless steel (SS) tube heating element that can activate the temperature-sensitive PCM valve using an externally applied radio-frequency (RF) magnetic field from a wearable device. Using in vitro and in vivo models, we demonstrate a large dose drug delivery capability of our A2D2 using a RF magnetic field generator as a proof-of-concept.

2. Materials and methods

2.1. Design and fabrication

The design of the device is shown in Fig. 1a. The fabrication steps of device are shown in SI Fig. 1. The simple device had four commercially-available and biocompatible components: a high-density polyethylene (HDPE) tube, a PTFE ball seal, stainless steel (SS) tube heating element, and a PCM (PureTemp 42, PureTemp, Minneapolis, MN, USA). The device was fabricated with a 8-mm-long HDPE tube (OD = 2.8 mm, PICS-501-MPIS-NT, Cook Medical, Bloomington, IN, USA), which is sealed in one end with press-fitted 3-mm-diameter PTFE sphere (McMaster-Carr, Elmhurst, IL, USA). The SS tube was obtained by cutting a 10-gauge stainless steel metal dispensing tip (Nordson EFD, East Providence, RI, USA) into 3-mm-long section. The drug was then inserted into the HDPE tube along with a SS heating element and sealed using approximately 3 g of PCM, which is designed to melt at 42 °C.

2.2. Device operation

The device is designed to be implanted subcutaneously using a trocar in a method similar to the insertion of a sub-dermal RFID tag. The drug is released when a high frequency magnetic field is applied over the implant site from a wearable magnetic field generator (Fig. 1b). The oscillating magnetic field causes induction heating of the

SS tube, which melts the PCM and allows the drug to diffuse out (Fig. 1c).

2.3. Heating element analysis

To evaluate the effectiveness of stainless steel heating element, we used FLIR A325SC thermal camera (FLIR, Wilsonville, OR, USA) to examine the time to reach the activation temperature for drug delivery (42°). The radio frequency (RF) magnetic field (270 kHz) was generated using a custom transmitter circuit that consisted of a 7-turn, 15-cm-diameter electromagnetic coil, a matching circuit, and signal generator, and a power amplifier to apply 30 kA/m of magnetic field. To demonstrate a wearable magnetic field generator, a low-cost ($13) commercial portable induction heater circuit (Yosoo ZVS Driver Circuit, Amazon.com) coupled with a portable battery (Suaoki P6, Shenzhen, China) were used (Fig. 1b). To characterize the time to heat SS up to 42°, the melting temperature of PCM, we placed our device in a water jacketed saline in vertical and horizontal positions and applied RF magnetic field from various distances ranging from 0.5 to 2 cm to mimic various implantation depth.

2.4. Leakage test

To quantify the stability of the device packaging, we measured the amount of leakage from devices filled with either powder or liquid drugs (n = 5, each) when submerged in a body temperature phosphate buffered saline (0.1 M, PBS, pH 7, Fisher Scientific, Waltham, MA, USA). We placed each device in a beaker filled with 50 mL PBS and stored them at 37 °C in a mixing chamber rotating at 200 rpm for 42 days. At time intervals 1, 10, 100, 100 h, we sampled 1 mL of PBS from each beaker for analysis and replaced with 1 mL of fresh PBS. At the end of the storage period, we measure the concentration of acetaminophen from each sample interval using spectrophotometric analysis (μQuant, BioTek Instruments, Inc., Winooski, VT, USA).

2.5. In vitro drug release

To identify the optimum device orientation that elicits the fastest drug release, we quantified the amount of released drug over time using two different device alignments (i.e., vertically aligned vs. horizontal to RF coil). For powder payload, we packaged each device with 12 mg of acetaminophen (A7085, Sigma-Aldrich, St. Louis, MO, USA). For liquid payload, 20 μL of acetaminophen solution (14 mg/mL) was dispensed into each device (Table 1). Each device was placed in a water-jacketed beaker containing deionized (DI) water (Milli-Q A10, Millipore, St. Louis, MO, USA) at 37 °C. A custom fixture was used to hold each device either vertically or horizontally 10 cm away from the top of the RF coil. The bespoke RF generator was turned on for 60 s at 270 kHz and the DI water was sampled (100 μL) every 15 s for the first 90 s, then every 1 min for the next 10 mins. After each sampling, the same amount of DI water was added to replace the lost volume. A spectrophotometer was used at λ = 243 nm to quantify the concentration of acetaminophen at each time point.

2.6. In vivo payload release

To visualize the drug release mechanics in vivo, we used a fluorescent imaging system (Spectral AMI HT, Spectral Instruments Imaging, LLC., Tucson, AZ, USA). We fabricated three devices with 20 μL of indocyanine green dye (ICG, Fisher Scientific, Waltham, MA, USA). To aid in the quantification of released drug amount, we created a standard curve using the ICG dye with concentrations ranging from 2 μg/mL to 25 μg/mL (SI Fig. 2). We subcutaneously implanted each device into 3 male C57BL/6 mice obtained from an in-house colony. Each animal was anesthetized with an initial injection of Buprenorphine (0.05–0.1 mg/kg) and with 1–3% Isoflurane in 1 L/min O_2 during the implantation,
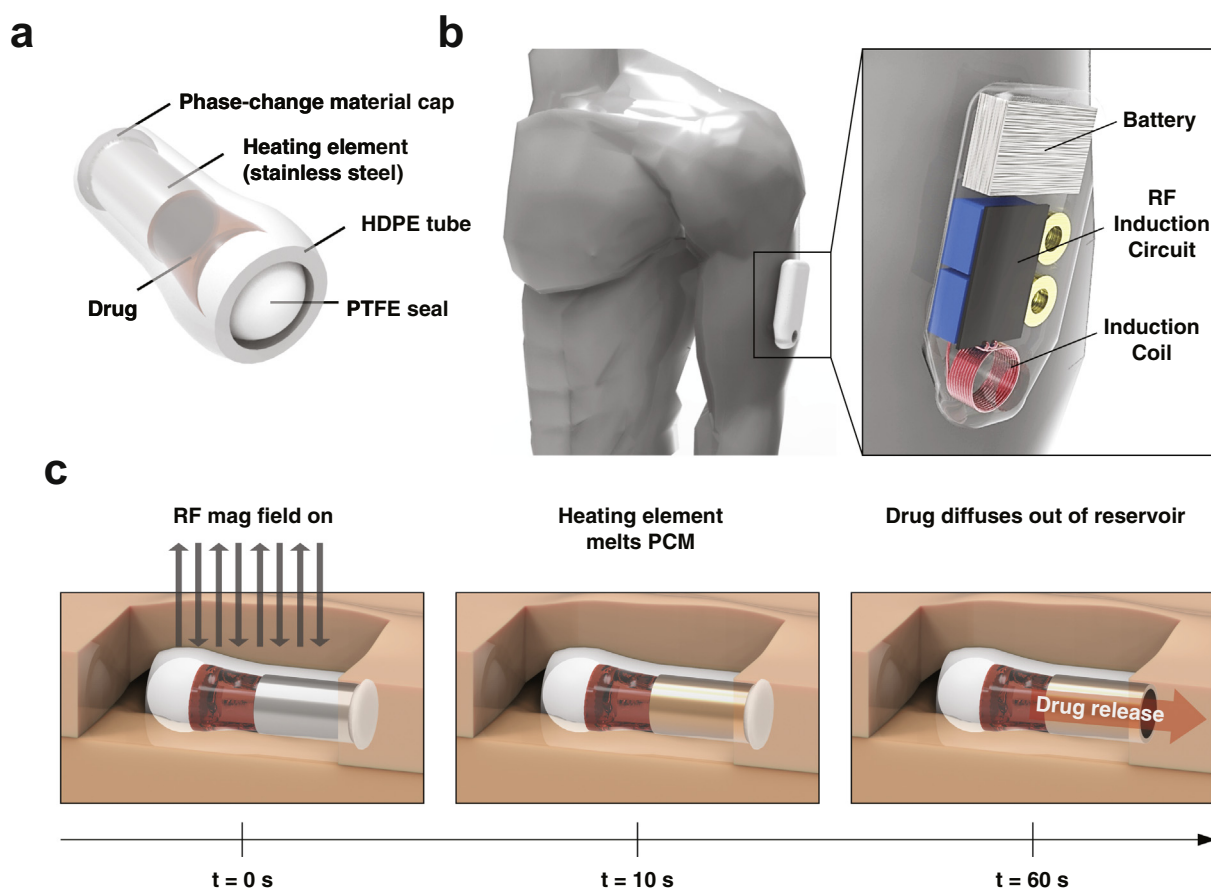
Fig. 1. (a) 3D model of the drug delivery device. (b) Schematic of wearable magnetic field generator used to release the drug. (c) When time-varying magnetic field is applied over the subcutaneously placed device, it allows the heating element to reach the melting temperature of the PMC and allows the drug to diffuse out in seconds.

device activation, and imaging. For implantation, a 1-mm incision was made in the left dorsum and the skin was separated from underlying connective tissue to create a subcutaneous pocket. The device was then inserted into the pocket and the incision sutured closed. After the implantation, mice were imaged every 10 min for 40 min prior to the activation of the implanted device to quantify any drug leakage. We then activated each device for 60 s using our bespoke magnetic field generator, and each animal was imaged for an additional 30 min post-activation. All procedure were performed with approval from the Purdue Animal Care and Use Committee.

3. Results

3.1. Device fabrication

Fig. 2a shows a photograph of a fabricated device. We fabricated a total of 44 samples filled with acetaminophen powder to gauge manufacturability. On average, our device measured to be 166.6 ± 5.3 mg with the weight of the drug was measured to be 11.5 ± 0.9 mg. SI Fig. 3 shows the weight of each device at various stages of fabrication.
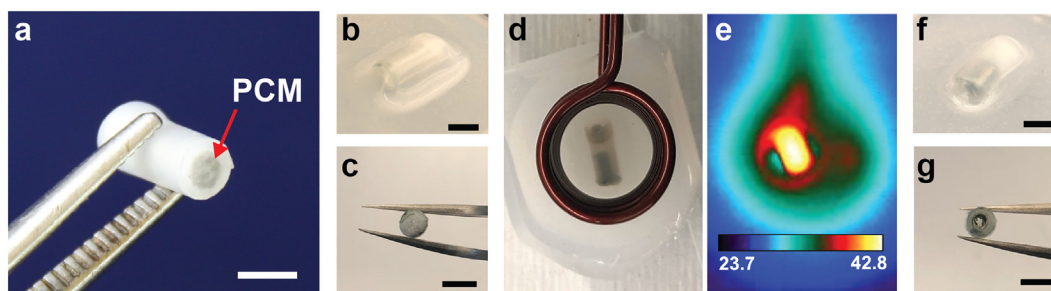
3.2. Device operation and heating element analysis

Fig. 3a show an example of wearable electrocardiography (ECG) sensor that can measure respiration rate [24]. Upon detection of significant respiration depression, which indicates opioid overdose, we can trigger the activation of a wearable RF generator to release the A2D2. Fig. 3c-d shows a proof-of-concept wearable magnetic field generator fabricated using off-the-shelf induction heater circuit packaged with a portable battery. The commercial ZVS circuit was able to deliver 16 kA/m of magnetic field at 195 kHz.

To characterize the performance of the heating element, we used a custom desktop RF magnetic field generator with a power amplifier and a frequency-matched induction coil to heat the SS heating element and measured the time to reach 42 °C needed to release the drug reservoir (Fig. 4a). Fig. 4b shows IR images of horizontally-aligned device 1 and 10 s upon application of RF magnetic field from 1 cm away. The commercial ZVS circuit required approximately 14.4 ± 3.9 s to reach 42 °C from 5 mm away at room temperature (SI Fig. 4). When a custom RF generator was used, the heating element reached 42 °C in 10 s to open the drug reservoir as can be seen from Fig. 4c. At the same time, the

Table 1
A summary of the in vitro drug release tests.

Acetaminophen form	Orientation	n	Release amount [mg]	% released	Equivalent naloxone [mg]
Powder [12 mg]	Vertical	10	8.80 ± 0.60	73.33	8.80 ± 0.60
	Horizontal	10	4.85 ± 0.60	40.42	4.85 ± 0.60
Liquid [0.7 mg]	Vertical	10	0.60 ± 0.10	85.71	2.14 ± 0.36
	Horizontal	10	0.67 ± 0.08	95.71	2.39 ± 0.29

Fig. 2. Photograph of A2D2 (a) and the demonstration of PCM dissolution using an induction coil (b-g). (b) The device was inserted in between phantom skin layers (1-mm-thick, Ecoflex 0030) to mimic subcutaneous depth. (c) The PCM cap maintains its solid form prior to activation. (d) Photograph of the induction coil placed 1 cm above the artificial skin. (e) Infrared image of the induction heating coil and the device. Temperature in celsius. (f) Image of the activated device under the artificial skin. (g) After the activation, the PCM cap melts and exposes the drug reservoir. Scale bars = 5 mm.

temperature of the surrounding solution remained near 37 °C, which ameliorates potential concerns for heat-induced damage to surrounding tissue in situ.

Fig. 4d shows the time taken to reach 42 °C at various distances from the custom RF coil. As expected, smaller distance between the coil and the device led to a shorter activation duration to reach 42 °C. At 1 cm, it required 12 ± 4 s to reach the desired temperature ($n = 5$). The time to reach 42 °C drastically increased as the distance grew from 1 to 1.5 cm, which may indicate an operational limit of our system. In terms of the device orientation, the time taken to reach the desired temperature did not differ much (Fig. 4e). We found that vertically aligned sample required 10.33 s to reach 42 °C and 11.4 s when aligned horizontally.

3.3. Leakage test

SI Fig. 5 shows the leakage test observed for the powdered device. After 1000 h, 0.21 ± 0.2 mg of powdered drug the amount leaked from the powder carrying devices (~2% of the total payload). Conversely, 0.1 ± 0.2 mg of liquid drug leaked from the device (~14% of the total payload). The amount released for both types of drug formulation is less than a single dose equivalent of naloxone to elicit a physiological response (0.4 mg) [25], however, the leakage may continue if the devices were incubated for longer period.

3.4. In vitro drug release

Fig. 5 show the results of the concentration release tests. The samples filled with powdered drug released an average of 4.85 mg (40% of

total payload) when tested horizontally and 8.80 mg (73% of total payload) when tested vertically in the span of 500 s. The samples filled with liquid released nearly all of their total drug volume by 300 s. Although the time to threshold temperature is similar for both horizontally and vertically aligned devices, the vertically aligned devices in general had faster release rates than the horizontal counterparts (Fig. 5). Within the first minute, the vertically aligned device released ~1.91 mg of powdered acetaminophen while the horizontally aligned device only released ~0.73 mg. In contrast, the vertically aligned device released ~0.54 mg of liquid acetaminophen while the horizontally aligned device only released ~0.31 mg.

### 3.5. In vivo payload release

In the in vivo experiment, we focused on drug releasing mechanism at the point of device activation. To visually verify that the contents of the capsule diffuse out only after the activation, we carried out in vivo imaging of fluorescent probe. Fig. 6 depicts the in vivo application of device samples activated under the skin of mice. We observed virtually no fluorescence prior to the activation of A2D2. Once activated, there was an immediate increase in fluorescence captured by Spectral AMI HT, which indicates successful release of the payload into the subcutaneous space. It also reveals rapid signal near the caudal end of the device, suggesting the diffusion is almost immediate out of the opening of the device.

4. Discussion

Opioid overdose is a serious problem with deadly consequences that
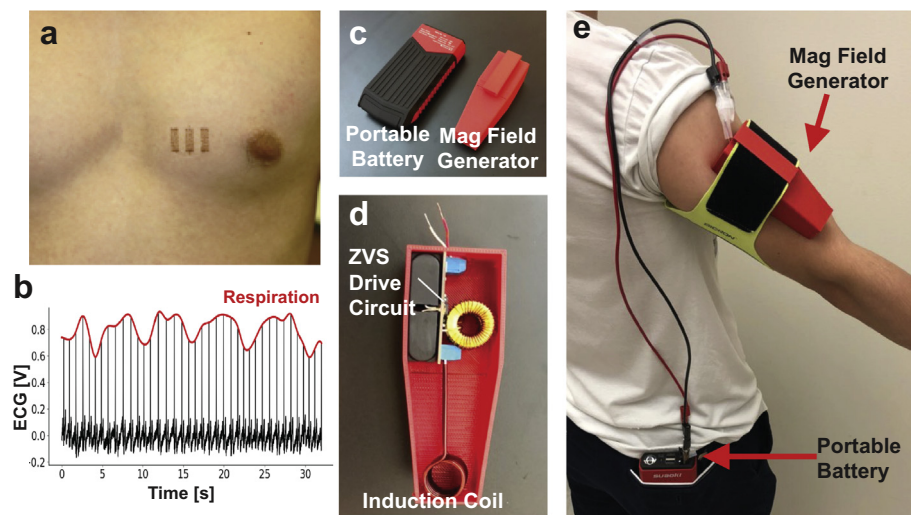
Fig. 3. Device operation and proof-of-concept portable magnetic field generator. (a) Photograph of ultraflexible ECG sensor that can measure respiration rate. (b) Using signal processing, respiratory signal may be derived from ECG data. (c) Photograph of a commercially available portable battery and magnetic field generator packaged with (d) an ZVS drive circuit. (e) Photograph of a user with the portable magnetic field generator.
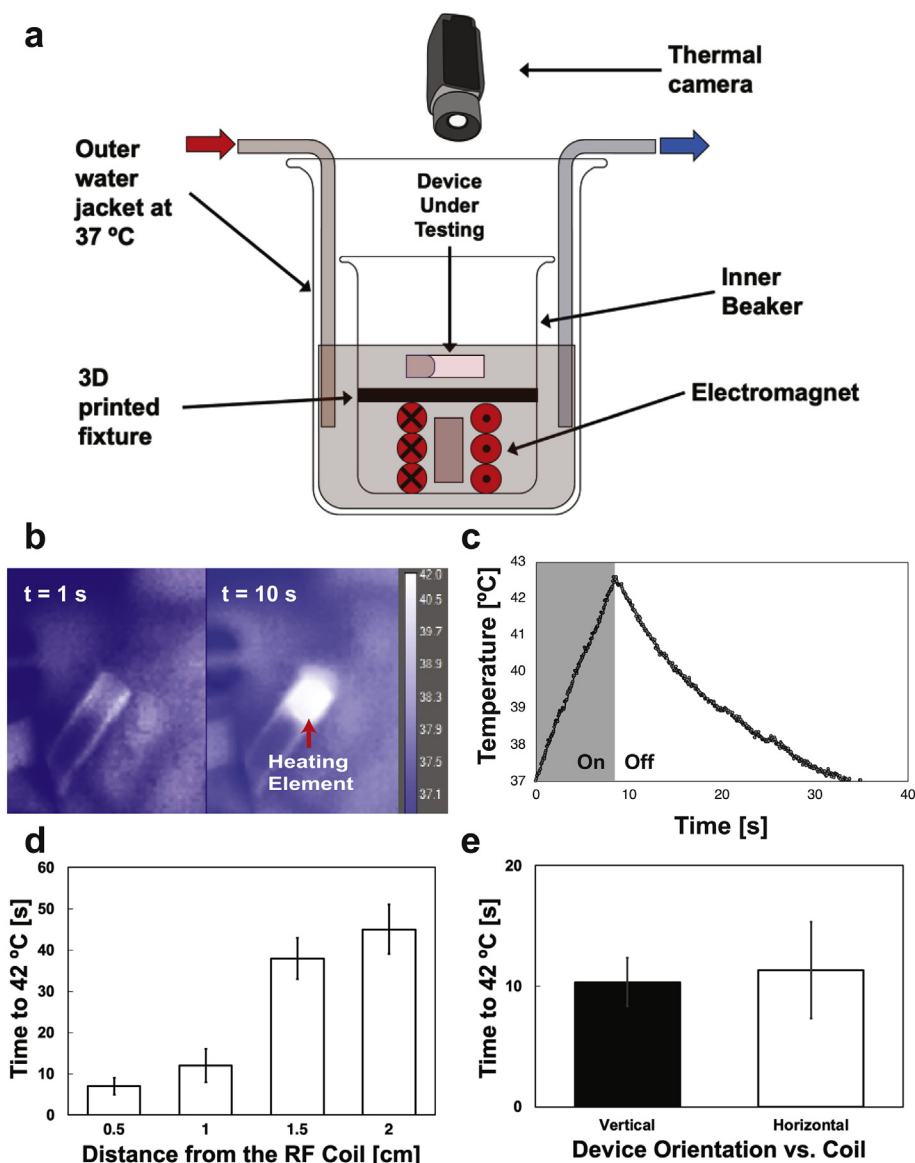
Fig. 4. Heating element analysis. (a) Schematic of bench-top evaluation. (b) Infrared images of a test sample at 1 and 10 s showing the heating element reaching 42 °C. (c) Plot of the horizontally aligned SS heating element temperature over the course of 10 s magnetic field application from 1 cm away. (d) Time to reach 42 °C at various distances from the electromagnet coil. (e) Time to reach 42 °C from different device orientation vs. the coil.

we believe can be prevented with appropriate engineered solutions. In this work, we demonstrated the proof-of-concept for simple emergency drug delivery device that can extend the golden hour for patients who accidentally overdose. The minimally-invasive device is designed to be placed under the skin and automatically release antidote in response to opioid overdose. Our simple and low-cost drug delivery device packaging can ultimately be activated using a portable and wearable magnetic field generator to prevent overdose-related respiratory failure.

The size of the our A2D2 (2.8 mm diameter, 8 mm length) is comparable to that of existing subcutaneous drug implants such as PROZOR™ (Delpor, Inc., San Francisco, CA, USA) and IMPLANON® (Merck & Co., Inc., Whitehouse Station, NJ, USA). Similarly, our device may be placed percutaneously via a trocar or a biopsy needle in an outpatient setting. Although we envision multi-dose and slow-releasing versions in the future, we will need to establish a safe procedure to remove expired or used device. We may be able to use an analogous procedure to explant existing subcutaneous devices (i.e., small incision).

One of the important design criteria for emergency DDS is its

capability to rapidly and automatically deliver antidote. We found that the time to reach 42 °C for both vertically and horizontally aligned devices were not very different (10.33 s vs. 11.4 s). This may be because the non-axial components of the magnetic field from our electromagnet can still induce eddy current in our heating element when it is placed horizontally. This relatively fast heating time in horizontal orientation is desirable because we expect our device to be deployed in this manner in vivo.

At the same time, we need to prevent accidental drug release from external heat and momentary exposure to ambient electromagnetic fields. According to literature, hot weather may not be problematic since subcutaneous temperature is known to remain below 38 °C even after a prolonged exposure to extreme heat [26]. Furthermore, A2D2 requires approximately 10 s of high frequency (195–270 kHz) magnetic field (30 kA/m) to release the drug, which is several orders of magnitude larger than the guideline limit for public magnetic field exposure of 80 A/m [27]. Thus, we believe only the intentional application of appropriate magnetic field amplitude and frequency can lead to the activation of our device with the exception of device failure or leakage.
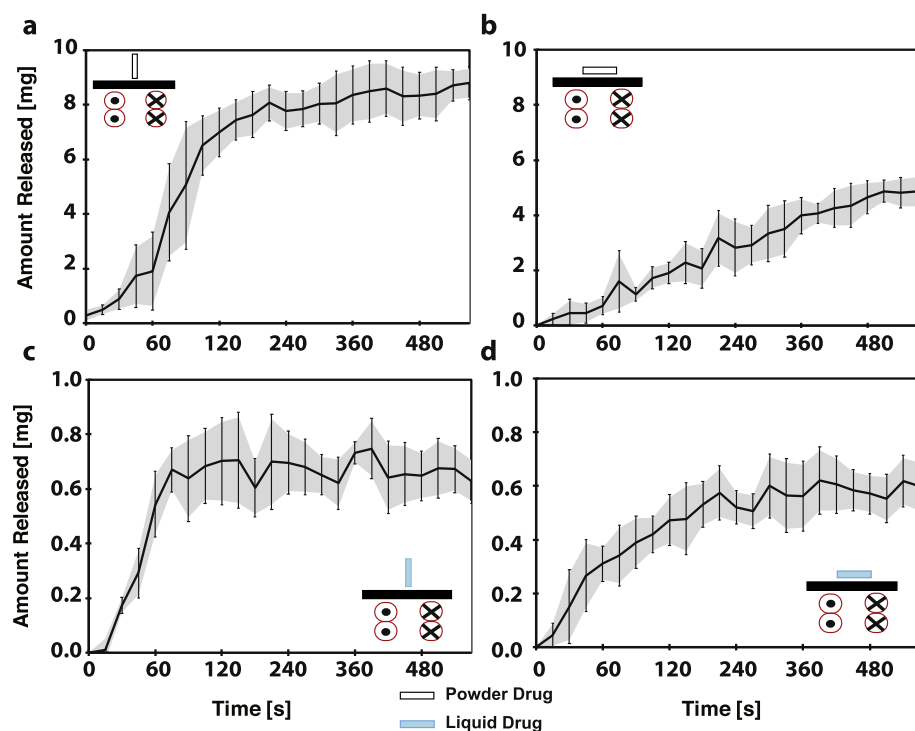
Fig. 5. Release profile of acetaminophen used in test samples during and post activation. The samples were submerged in 50 mL DI water. AC supply was switched on at $t = 0$ for 90 s. (a) Test samples placed horizontally on test fixture with liquid drug. (b) Test samples placed vertically on test fixture with liquid drug. (c) Test samples placed horizontally on test fixture with powdered drug. (d) Test samples placed vertically on test fixture with powdered drug. Note that samples with liquid drug release all of its content within ~100s. In comparison, the release profile of powdered drug was much slower.

In our preliminary leakage test, we found that our devices had some leakage issue when exposed to a body temperature PBS for 1000 h. The leaked drug amount was approximately 0.21 mg and 0.08 mg for powdered and liquid forms of acetaminophen (SI Fig. 5). Drug leakage and stability are critical issues for emergency DDS. If no active drug is available at the time of opioid overdose due to leakage or drug degradation, it could lead to a devastating consequence for the patient. As such, additional evaluations are required to verify the robustness of the device packaging. Furthermore, we will need to evaluate the stability of the drug formation over the course of extended implantation to ensure that the antidote maintain its functionality.

In terms of device fabrication, the simple design allowed us to easily fabricate many samples ($n = 44$) to preliminarily gauge the manufacturability (SI Fig. 1). We expected a certain level of variability in the physical dimensions of hand fabricated devices (SI Fig. 3). One critical dimension for consistent drug release is the weight of PCM. We found that the weight of PCM to be 2.8 ± 1.05 mg, which likely have contributed to the variability in drug releasing speed and drug leakage. Although we expected PCM to melt around 42 °C based on the manufacture's datasheet, differential scanning calorimetry (DSC) showed that it melts around 46.5 °C (SI Fig. 6). This suggests that additional optimization will be needed to prevent any potential tissue damage (> 45 °C) and to reduce the release time. The DSC results also confirmed that the other components of A2D2 (i.e., PTFE and HDPE) will not be affected by the temperature increase. In the future, we may also use radio-opacifier (e.g., barium-sulfate) impregnated HDPE to better track the implant in vivo in case of device migration [28].

The total amount of drug that can be delivered from A2D2 depends on the formulation given the payload volume (0.2 μL), and this capacity may easily be adjusted by changing the dimensions of the HDPE capsule. However, we found that in general the liquid formulation can release its full payload faster than the powdered version. In certain cases, powdered drug did not fully release its payload presumably due to clumping and aggregation inside the device post-activation. Moreover, the horizontally-aligned devices, which better mimic the implant orientation in vivo, had slower release profiles compared to the rapid burst release seen in the vertically-aligned devices. Nevertheless, we showed that both liquid and powder forms can release

approximately 0.31–1.91 mg of acetaminophen within 60 s of activation. Since naloxone has a higher solubility than acetaminophen (50 mg/mL vs. 14 mg/mL), this is equivalent to approximately 1.11–1.91 mg of naloxone or 2.77–4.78 doses (0.4 mg/dose) [25].

For emergency drug delivery, it may be ideal to provide a rapid burst of the antidote (Fig. 5a,c,d). However, a more prolonged high-concentration drug release afforded by the powder formulation in the horizontal orientation (i.e., zero-order release, Fig. 5b) may also be beneficial because many patients often relapse back into overdose due to insufficient initial dose of naloxone. It may be interesting to combine the liquid and powder formulations in a multi-lumen form to facilitate both rapid and sustained high dosage delivery of naloxone. Although there are some concerns of opioid withdrawal syndrome with a large administration of naloxone, literature suggests that even extreme concentration of naloxone may be given to patients without potential morbidity and mortality [29]. Thus, the large capacity version of A2D2 may help prevent patients from relapsing back into overdose while they await emergency medical care.

To demonstrate the wireless activation of A2D2 in vivo, we implanted ICG-filled A2D2 in mice and observed the payload releasing profile over time. Based on literature, we presumed that naloxone released in the subcutaneous space will have the same clinical effect as intravenous and intramuscular injection [8,30]. Therefore, we used the in vivo payload release experiments to demonstrate the capability to deliver drug on demand. Prior to the activation signal, we observed no leakage in any of the devices during this 40-min-period. Once activated, we saw an instant increase in fluorescence and the maximum radiance by 20 min. The fluorescence signal appeared from the PCM end of the capsule, which suggests that the releasing mechanism worked as designed. Although additional in vivo evaluation is required to determine the capability to actually reverse opioid overdose using this device, we believe these preliminary results highlight the possibility of rapidly releasing antidote on demand during an emergency.

Ultimately, the goal of this work is to close the loop in opioid overdose treatment by detecting the onset of overdose using physical or chemical biomarkers and releasing the antidote in response to prevent accidental opioid overdose. In this work, we demonstrated the feasibility of using subcutaneously placed A2D2 that can deliver a large
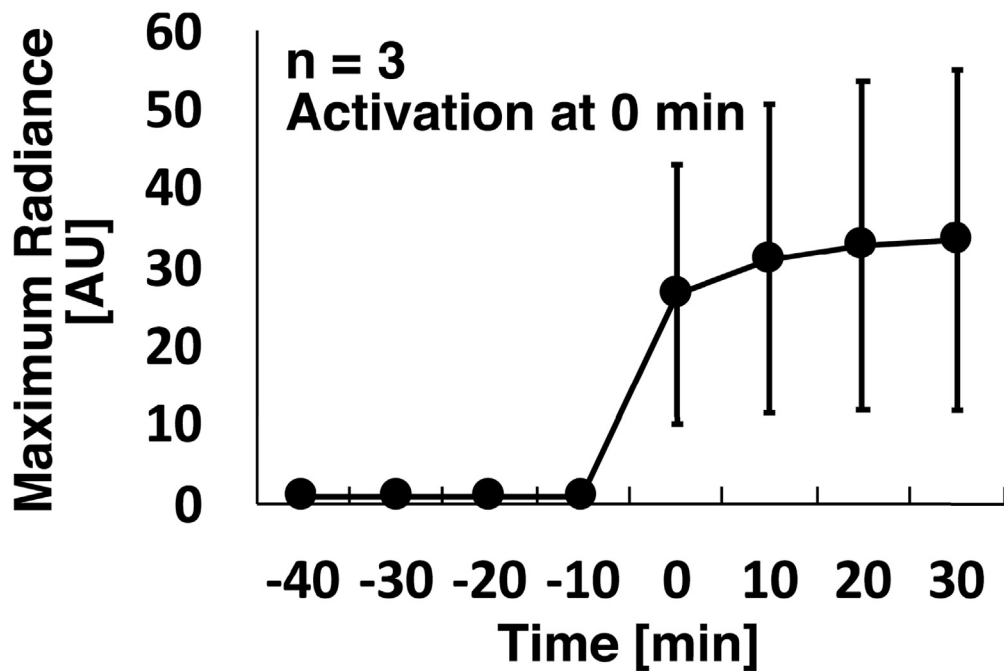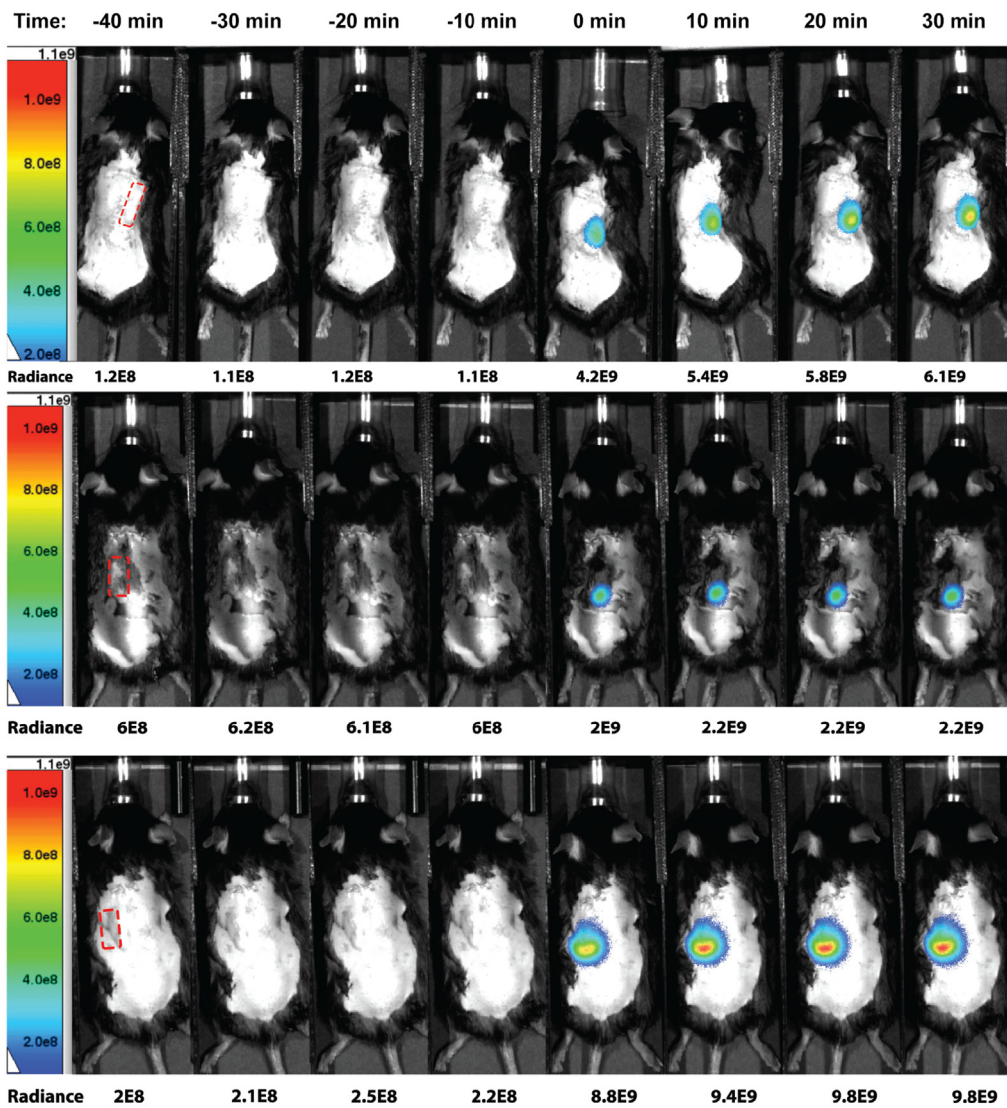
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Fig. 6. Top: Fluorescent images of the animal during the pre-activation period (− 40 min to 0 min), at activation (0 min) and following activation (0 min to 30 min). Bottom: Normalized radiance values from 3 mice tested. The pre-activation images show no leakage in the first 40 min of device implantation. Following activation, we saw an immediate spike in the fluorescence which stabilized by 10 mins.

amount of antidote on demand. We used a commercial ZVS circuit to demonstrate the proof-of-concept for a wearable device that can deliver a short burst of high frequency magnetic field to release the drug. We envision a system that integrates the wearable physiological monitor (Fig. 3a-b) that can be fed into a microcontroller to switch on the ZVS circuit when the respiration rate drops below a threshold to wirelessly trigger the drug release from A2D2 (SI Fig. 7). When successful, we believe this closed-loop system may have a great impact not only for opioid overdose but for many other emergency drug delivery applications (e.g., epinephrine, atropine).

5. Conclusion

Here we demonstrated the design, fabrication, and evaluation of a simple automated antidote drug delivery device that could potentially be placed subcutaneously for rapid antidote release following an accidental opioid overdose. Our bench-top evaluations showed its capability to rapidly release its payload using externally applied time-varying magnetic fields. Furthermore, our in vivo evaluation demonstrated successful on-demand, wireless activation of our devices. Additional experiments are planned to demonstrate the device's capability to reverse opioid overdose and to integrate wireless respiratory monitor for closed-loop antidote release.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2019.05.041.

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