SOFT INJECTABLES USING SMART THREADS FOR DOSE-CONTROLLED DRUG DELIVERY

Mossab K. Alsaedi[1,2], Riddha Das[1,3], Hojatollah Rezaei Nejad[1,3], Atul Sharma[1,3], and Sameer Sonkusale[1,2,3,4]*
[1]Nano Lab, Advanced Technology Laboratory, Tufts University, Medford, Massachusetts, USA
[2]Department of Chemical and Biological Engineering, Tufts University, Medford, Massachusetts, USA
[3]Department of Electrical and Computer Engineering, Tufts University, Medford, Massachusetts, USA
and [4]Department of Biomedical Engineering, Tufts University, Medford, Massachusetts, USA

ABSTRACT

Transdermal drug delivery is a promising alternative to conventional drug delivery approaches, such as oral ingestion and hypodermic injection. Hypodermic injections are often painful, and oral ingestion of drugs requires the administration of doses higher than the needed to compensate for enzymatic degradation and poor absorption of drugs. Current transdermal drug-delivery platforms include microneedles, which resolve the pain aspect of conventional drug delivery approaches. However, microneedle patches are impractical as they are easily peeled off with motion and sweat. In this study, we propose soft injectables comprised of sutures that are loaded with drugs for painless and localized sustained drug delivery in the dermis layer of the skin. They stay in place during the course of delivery and are suitable for any skin type.

KEYWORDS

Transdermal drug delivery, smart threads, sutures, injectables, chemotherapy, implants, drug delivery.

INTRODUCTION

Oral administration of drugs often results in poor absorption and suffers from enzymatic degradation in the liver or the GI tract that reduces their efficacy [1,2]. The alternative is a painful injection using hypodermic needles. Transdermal delivery using microneedles offers a relatively painless route of drug delivery through interstitial fluid, where the release of drugs can be sustained over long periods of time and tuned through size, number, and matrix composition of microneedles [2,3] (Figure 1). However, microneedles can still cause skin inflammation, may not penetrate reliably in all skin types, are prone to breakage, and can peel off due to sweating or motion, which makes them highly unreliable for drug delivery. We propose *soft injectables,* which are drug-loaded sutures for drug delivery through the interstitial fluid. Like microneedles, they are painless, as they are injected in the dermis layer of skin using fine needles. Unlike microneedles however, they are not prone to being peeled off with motion or by sweating and do not cause inflammation as they are realized using medical-grade sutures as substrates. Use of threads for drug delivery in the context of wound healing [1] and as sutures [4,5] was investigated by our group, and by others [6], however they were not used as injectables. Soft injectables using threads provide precise control over drug quantity by simply controlling their lengths. While transdermal applications have been proposed, threads can also be implanted in deeper organs/tissues as implants.

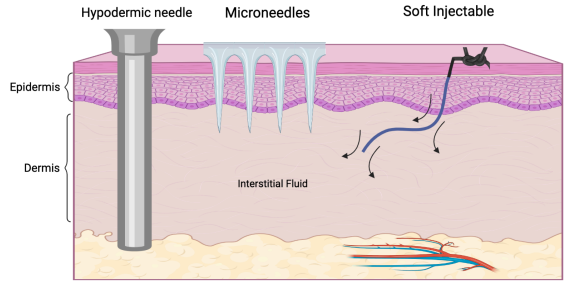

Figure 1. Illustration and comparison of transdermal (microneedles and injectable) and dermal drug delivery platforms.

In this study, we introduce a new class of thread-based injectables for dose-controlled drug delivery demonstrated by using rhodamine B (model dye) and *in-vitro* experiments with 5-Fluorouracil (5-FU), which is a cancer drug, and studying its release on cancer cells.

APPROACH

The approach uses natural wetting of threads to load the drugs onto them. Threads are made of multiple fibers that are combined and woven together. These fibers can be natural fibers, such as silk and cotton, or synthetic ones, such as polyester and nylon [7]. Hydrophilicity and wettability are two important properties of threads when it comes to drug loading. Different surface chemistries and structural morphologies of threads result in their varying wettability degrees [7]. Therefore, surface plasma treatment (surface oxidation) is used to increase threads' wettability and hydrophilicity [7]. Furthermore, the uniformity of a thread's surface allows for more precise wetting [8]. In addition to selecting the thread with the appropriate surface uniformity and wettability, the length of the thread can also be controlled to control amount of drug loaded and released.

A drug-loaded, thread soft injectable can be administered in different ways. It can be inserted through a catheter tube after the tube reaches the desired depth. It can also be sutured in through the skin using a fine surgical needle, keeping part of it on the surface of the skin to hold the injectable in place. Because these injectables are soft and flexible, they would be less painful and more stable when kept in place during the course of drug delivery compared to rigid microneedles. The microneedles, being rigid patches on the surface of the skin, do not conform to the soft and flexible nature of the skin and the underlying tissue.

We propose the use of the soft injectables for delivery of 5-FU, which is a common drug that is used to treat a wide range of cancers, including breast cancer and aerodigestive-tract cancers, and is administered intravenously [9]. It is converted to active metabolites upon entering a cell. Its cytotoxicity is attributed to the active metabolites' hindering RNA synthesis and inhibiting thymidylate synthase enzymes in cancer cells [9]. In our case, 5-FU can be delivered to cancer tumors, such as skin cancer, through drug-loaded injectable threads rather than the more invasive intravenous approach or painful microneedles.

EXPERIMENTAL METHODS

Drug loading onto medical-grade threads

First, we evaluated the drug-loading capacity of different

978-1-940470-04-7/HH2022/$25©2022TRF
DOI 10.31438/trf.hh2022.36

Solid-State Sensors, Actuators, and Microsystems Workshop
Hilton Head Island, South Carolina, June 5-9, 2022

available thread type: polyester threads, cotton threads, polyester sutures, and Polysorb™ sutures. Specifically, the wet and dry weights of threads were compared. All threads were first plasma treated for 10 minutes. Then, they were weighed before being submerged in deionized (DI) water overnight. The threads are then weighed again after being in water overnight. Difference in weight before and after submerging threads in water is then calculated to generate the bar chart in Fig. 2.

Visual monitoring of drug release from thread

To visualize drug-release mechanism into biological tissue, we visually monitored the diffusion of rhodamine B from a polyester suture into an agarose gel. A 2-cm polyester suture was plasma treated for 10 minutes then submerged in a 1 mg/mL rhodamine B-DI water solution overnight. The suture is then dried in ambient air for at least 6 hours. Once the suture is dry, it is inserted in an agarose gel (2% w/v agarose in 1X phosphate-buffered saline (PBS)). Images of the agarose gel are taken at 0, 5, and 10 minutes from inserting the suture (Fig. 3).

Dose-controlled release of 5-Fluorouracil from sutures

We evaluated the total drug release as a function of thread length to elucidate controlling drug dose by controlling thread length. 5-FU release profile was obtained by first submerging plasma treated sutures of lengths 0.6 cm, 6 cm, and 60 cm overnight in 4 mg/mL 5-FU solution (in 1X PBS). The sutures are then dried in ambient air for at least 6 hours. Then, the sutures are put in 1X PBS. Ultraviolet visible spectroscopy (UV-Vis) measurements of the solution containing the 5-FU-loaded sutures are obtained at 5, 15, 30, 60, 150, and 240 minutes from submerging the suture in 1X PBS. UV-Vis spectra were used to generate the release profile in Fig. 4.

Cancer-cell viability study with chemotherapeutic injectables

Lastly, we released a cancer drug from threads into cultured cancer cells to demonstrate biocompatibility and effective dose-controlled drug release by analyzing cell viability. Loading 5-FU on 2, 3, and 4 cm sutures for cell viability studies follows the same procedure previously mentioned for 5-FU release profile. However, the sutures are submerged in 12 mg/mL solution of 5-FU in DI water instead of 1X PBS. Once sutures are dry, they were sterilized under UV light for 2 hours then added to cultured HeLa cells for 48 hours of incubation. Fluorescence measurements produced the cell viability data in Fig. 5.

RESULTS AND DISCUSSION

Threads' uptake

We compare different threads for their drug loading capacities by assessing their water uptake. Fig. 2 shows results using non-resorbable polyester and cotton threads, polyester sutures, and resorbable Polysorb™ sutures. Loading capacities are attributed to the threads' surface properties. Cotton consists of less organized fibers with more open pockets that can take up more fluid, but random topography results in less control over amount (error bars in Figure 2e). Polysorb™ sutures also exhibit less uniform uptake (error bars in Figure 2e). For purpose of demonstration, we chose polyester sutures for their uniform drug loading capacity. Water uptake of polyester thread, polyester suture, cotton thread, and Polysorb™ suture: 28.1±4.66 µg/mm, 57.9±10.3 µg/mm, 229±18.4 µg/mm, and 506±288 µg/mm, respectively (n=7).

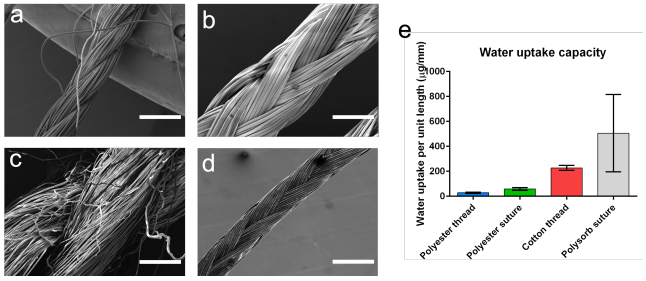

Figure 2. Water uptake is correlated to thread fiber organization. SEM images of (a) polyester thread (b) polyester suture and (c) cotton thread (d) Polysorb™ suture (scale bars = 300 µm). (e) Water uptake of polyester thread, polyester suture, cotton thread, and Polysorb™ suture (n=7).

Visual monitoring of dye diffusion from polyester suture

The diffusion of a model drug, rhodamine B dye, from soft injectable sutures was monitored to help visualize the drug-release mechanism into biological tissue. Fig. 3 shows a time lapse of the dye's release profile into an agarose gel, which is the artificial skin model in this study. All the dye that was loaded on the suture diffused from the thread into the surrounding agarose gel in only 10 minutes.

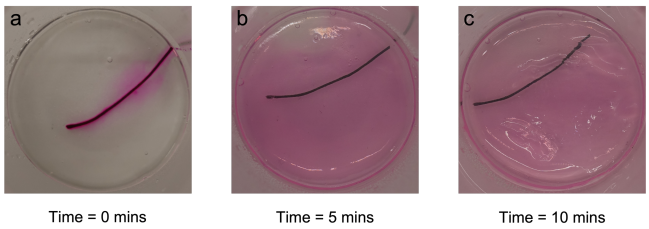

Figure 3. Visual monitoring of model drug - rhodamine B dye: shows drug diffusion off injectable (namely drug loaded polyester suture) in skin model made from agarose gel matrix (a) when suture is initially inserted (at 0 minutes), (b) after 5 minutes, (c) after 10 minutes.

Dose-controlled release of 5-Fluorouracil from sutures

To show control over quantity of drug released by controlling suture length, 5-FU was released in 1X PBS from suture of different lengths. Sutures of lengths 0.6 cm, 6 cm, and 60 cm each released different quantities of 5-FU. These lengths were chosen for characterization and to correlate thread's length with amount of drug released. The longer the suture is, the more 5-FU it released, which is attributed to the increase in drug loading with increasing suture length. Fig. 4 shows the release profile of 5-FU in from drug-loaded sutures of different lengths in the first 240 minutes after the suture was submerged in 1X PBS. Total amount of drug released after 240 minutes from 0.6 cm, 6 cm, and 60 cm long sutures is 0.0193±0.000438 mg, 0.0470±0.0148 mg, and 0.431±0.0543 mg, respectively (n=3). It is inferred from Fig. 4 that the majority, if not all, of the loaded drug is released within the first 15 minutes. Whereas releasing 5-FU from microneedles achieves less than 5% cumulative permeability in the first 10 hours [10].

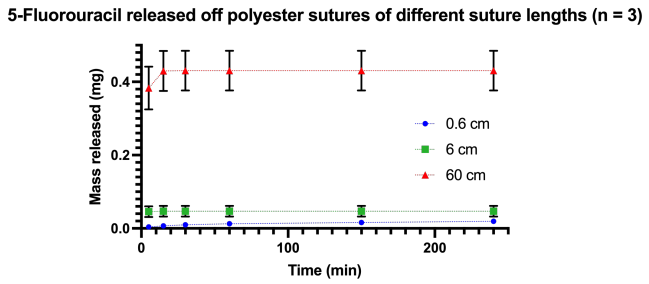

Figure 4. Longer threads release more drugs. The release profile of 5-Fluorouracil from injectables made from drug-loaded polyester sutures (0.6 cm, 6 cm, and 60 cm length) in 1X PBS over the period of 240 minutes.

Drug delivery with chemotherapeutic injectables

HeLa cells were chosen as cancer cell model to study *in-vitro* drug release. 5-FU-loaded injectable sutures showed considerable reduction in cell viability compared to bare threads, demonstrating successful drug delivery from polyester threads (Fig. 5a). Furthermore, polyester-suture injectables demonstrated excellent biocompatibility. Cell viability after 48 hours of being in contact with bare sutures was 99.1±2.83%, 93.9±1.87%, and 93.1±12.8% for bare 20 mm, 30 mm, and 40 mm long sutures, respectively. The 5-FU-loaded soft injectables demonstrated lower cell viability with higher suture length, which is attributed to the increase in amount of drug released with increasing suture length. The cell viability after 48 hours of being in contact with drug-loaded injectables was 67.9±2.46%, 64.7±5.09%, and 50.6±2.90% for 20 mm, 30 mm, and 40 mm long sutures, respectively. The number of dead HeLa cells after 48 hours of being in contact with a bare suture and a drug-loaded suture can also be visually compared under the microscope (Fig. 5b and 5c). These results demonstrate the potential of utilizing the threads for drug delivery.

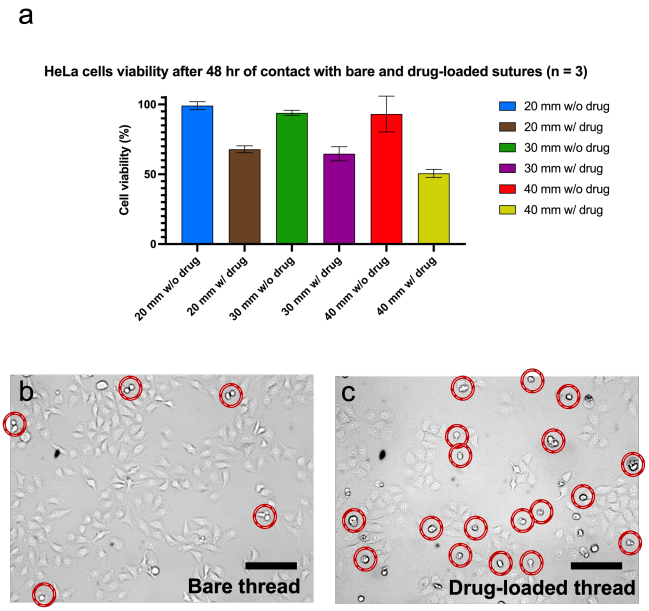

Figure 5. Soft injectables are biocompatible, and when loaded with chemotherapeutic drugs, decrease viability of cancer cells when in physical contact. (a) Cell viability of HeLa cells with the presence of bare polyester sutures as injectables and drug-loaded injectables (5-Fluorouracil loaded onto 20 mm-, 30 mm-, and 40 mm-long sutures) after 48 hours of incubation. The cell viability in presence of drug-loaded sutures was reduced considerably due to the release of the drug. Microscope images of cultured HeLa 48 hours after being in contact with (b) bare polyester suture and (c) drug-loaded polyester suture. Dead cells are circled in red. All scale bars are 80 μm.

CONCLUSION

Soft injectables can substitute conventional and painful drug delivery methods, such as using hypodermic needles, or unreliable methods, such as using microneedles or oral ingestion. In this study we explore medical-grade polyester sutures as soft injectables for transdermal drug delivery. Sutures are coated with drugs through wetting. Polyester sutures show appropriate and uniform loading capacity. Controlling the injectables' length allows for the control of the drug dose released. The release of a model drug (rhodamine B dye) was qualitatively analyzed, and the release of a cancer drug (5-fluorouracil) was quantitatively analyzed. Furthermore, chemotherapeutic soft injectables were explored. They demonstrated biocompatible properties and successful release of 5-fluorouracil within cultured cancer cells environment, resulting in lower cancer cell viability, as expected with increasing injectables' lengths. This study showcases a new class of thread-based injectables for dose-controlled drug delivery.

REFERENCES

[1] P. Mostafalu et al., "A Textile Dressing for Tempotal and Dosage Controlled Drug Delivery", *Adv. Funct. Mater.*, 17023399, 27 (2017).

[2] M.R. Prausnitz and R. Langer, "Transdermal drug delivery", *Nature biotechnology*, 1261-8, 26, 11 (2008).

[3] H. Nejad, A. Sadeqi, G. Kiaee et al., "Low-cost and cleanroom-free fabrication of microneedles", *Microsyst Nanoeng*, 17073, 4 (2018).

[4] G. Kiaee et al., "A pH-Mediated Electronic Wound Dressing for Controlled Drug Delivery", *Adv. Healthcare Mater.*, 1800396, 7 (2018).

[5] S. Sonkusale and P. Mostafalu, "Thread-based integrated functional devices", U.S. Patent Application No. 15/749,207

[6] M. L. Hakim et al., "Local drug delivery from surgical thread for area-specific anesthesia", *Biomed. Phys. Eng. Express*, 015028, 6 (2020).

[7] W. Tan et al., "Go with the capillary flow. Simple thread-based microfluidics", *Sensors and Actuators B: Chemical*, 129670, 334 (2021).

[8] H. Rezaei Nejad, A. Sadeqi, and S. Sonkusale, "Thread as a precise sampling and delivery platform", *The 24th International Conference on Miniaturized Systems for Chemistry and Life Sciences (μTAS 2020)*, (2020).

[9] D. Longley, D. Harkin, and P. Johnston, "5-Fluorouracil: mechanisms of action and clinical strategies", *Nat Rev Cancer*, 330-338, 3 (2003).

[10] B. Yang et al., "Bilayer dissolving microneedle array containing 5-fluorouracil and triamcinolone with biphasic release profile for hypertrophic scar therapy." *Bioactive Materials*, 2400-2411, 6.8 (2021).

CONTACT

*S. Sonkusale, tel: +1-617-627-5113; sameer.sonkusale@tufts.edu