ON-DEMAND TRANSDERMAL DRUG DELIVERY PLATFORM BASED ON HOLLOW-GROOVE MICRONEEDLE ARRAY

Jihyun Kim, Danilo M. dos Santos, Hasika Suresh, Sameer Sonkusale
Department of Electrical and Computer Engineering, Tufts University, Medford, MA, 02155, USA
Nano lab, Tufts University, Medford, MA, 02155, USA

ABSTRACT

In this work, we demonstrate a precise drug delivery with a Hollow-Groove Microneedle (HGMN) array controlled by a micro pump. To overcome the limitation of the previous hollow microneedles, which can be blocked during tissue penetration, a new structure combining hollow and groove features was introduced. Our system controls the volume of drug released into the tissue by dispensing the drug stored in the reservoir to the back layer of the HGMN using a micro pump. To improve the stability and homogeneity of the drug during storage in the reservoir, the core-shell solid lipid nanoparticles (SLNP) were employed to encapsulate the drug. Herein, by combining SLNP with the HGMN platform, we can achieve precisely controlled delivery of nanostructured drug carriers for an advanced personalized drug-releasing device.

KEYWORDS

3D printed Microneedle, Hollow-Groove Microneedle (HGMN), Core-shell solid lipid nanoparticle (SLNP), Drug delivery system, Personalized wearable healthcare device.

INTRODUCTION

Microneedle arrays (MNAs) represent an innovative approach to drug delivery that involves a substrate with submillimeter-sized needles [1]. This system effectively delivers therapeutic compounds into the skin by bypassing the outermost layer, thereby reducing the side effects associated with traditional oral and intravenous drug administration. Hollow-structured microneedle arrays (HMNAs), a subtype of MNAs designed for drug release, facilitate the transfer of drugs from the reservoirs to the transdermal layer [2]. Previous research has explored various fabrication methods for HMNAs, including photolithography [3] and laser engraving [4], which necessitated multiple additional processes and accurate alignment to create the hollow structure. Not only the complicated fabrication process but also additional challenges arise during tissue penetration because the hollow edges can be obstructed by the tissue, leading to drug release failure. Furthermore, HMNAs relying on passive drug release lack an active control system, potentially leading to drug overdose or underdose [5]. To address this, studies have investigated active control systems combined with MNAs, such as pumps [6] and microfluidics [7]. Among these, the micro pump shows promise for miniaturized wearable systems to control drug dispensing [8] enabling precise drug delivery to MNAs. Nonetheless, the diffusion of drugs into the skin varies based on their hydrophobic or hydrophilic properties, posing challenges for hydrophobic drugs due to the predominantly aqueous nature of the human body. Herein, we present a 3D-printed HGMN array-based drug release system controlled by the micropump. To prevent hollow blockage during tissue insertion, we designed hollow structures with groove structures that allow drug release along the groove path. By fabricating hollow and groove combined structures using a DLP 3D printer, we eliminated complex procedures Additionally, to enhance the versatility of our system and ensure drug stability and homogeneity, we incorporated core-shell solid lipid nanoparticles as drug carriers. By incorporating these advancements, our system offers a promising approach for precise and controlled drug delivery, with potential applications in personalized medicine and wearable drug delivery devices

MATERIAL AND METHOD

Histological test

The tissue sample, inserted with the HGMN array, was washed three times with phosphate-buffered saline (PBS). To freeze the tissue entirely, the tissue sample was preserved in a 15 % sucrose solution for 1 hour and a 30 % sucrose solution overnight. After washing with PBS, the tissue sample was embedded in a plastic mold and filled with Tissue-Tek OCT compound. The bubbles formed during the pouring of the Tissue-Tek OCT compound was removed and the mold containing the sample was placed in a – 80 ℃ deep freezer. Subsequently, the prepared cryoblock was sliced to a 10 μm thickness and stained with hematoxylin and eosin (H&E) (ab245880, ABCAM, UK). The morphology of each sectioned tissue was imaged and captured with the optical microscope (VHX 7000, Keyence, Japan).

Releasing test with sulforhodamine B

As a skin-mimicked model, agarose gel was prepared by pouring melted agarose solution into the 35 mm by 10 mm petri dishes [9]. In this study, phosphate-buffered saline (PBS) based agarose gel with 1.7 % concentration was employed to improve the absorbance of the released solution. The restored sulforhodamine B in the reservoir was dispensed by the micro pump to the HGMN. The pump was operated using a pulse signal with a magnitude of 5V, a frequency of 0.1 Hz, and a 30 % duty cycle. The release process was conducted on the wet tissue to prevent the agarose gel from drying out. At three different time points, the HGMN was removed, and the agarose gels containing released sulforhodamine were immersed in 20 ml of deionized (DI) water for restoration. After melting the agarose gel in the DI water, the absorbance at 554 nm was measured with the UV-Vis spectrophotometer (ND-1000, Thermo Scientific, USA).

DISCUSSION

Overall Concept of the Platform

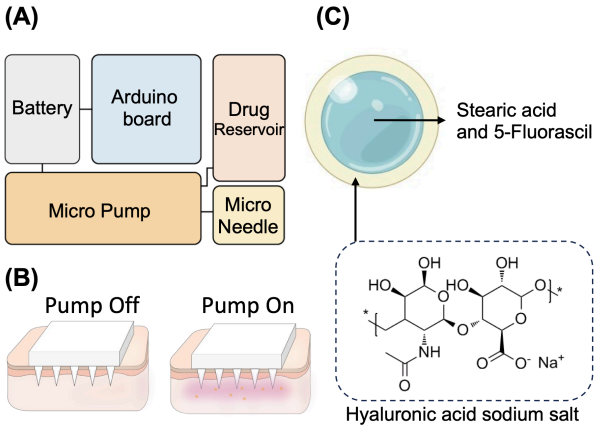

Figure 1 *(A) Schematic diagram of fully integrated drug delivery with micropump system. (B) Schematic of the drug releasing HGMN*

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with lipid nanoparticles. (C) Schematic representation of core-shell nanoparticles with a stearic acid core and a hyaluronic acid sodium salt shell and chemical structure.

This system comprises a Hollow-Groove Microneedle (HGMN) array controlled by a micro pump, consisting of the HGMN, drug reservoir, micro pump, Arduino board, and battery (**Figure 1(A)**). By connecting the inlet and outlet of the micropump to the HGMN and reservoir respectively, the drug can be dispensed from the reservoir to the HGMN. The micropump is controlled by an Arduino board allowing modulation of the duty cycle to control the volume dispensed into the HGMN. As illustrated in **Figure 1(B)**, the micropump-controlled release mechanism enables drug delivery into the tissue through the HGMN. For sustainable drug release, ensuring drug stability and homogeneity during restoration in the reservoir is crucial. To address these requirements, the drug was loaded with core-shell SLNP. In this study, we employed 5-Fluorouracil (5-Fluo) as a model of the drug for melanoma treatment.

Fabrication of the HGMN

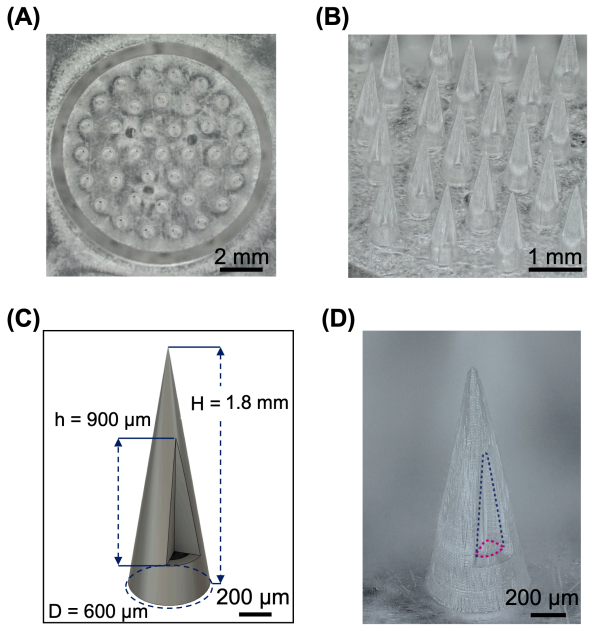

Figure 2 *Optical microscopic images of fabricated HGMN with 3D printer captured at (A) top-down and (B) titled view. (C) Schematic of proposed HGMN dimensions and (D) optical microscopic image of fabricated HGMN.*

As shown in **Figures 2(A) and 2(B)**, our HGMN array features two hollows in each microneedle connected to the groove, which enhances the drug flow following the grooved path and minimizes the risk of hollow blockage during tissue penetration. The HGMNs array was designed using Fusion 360 software and fabricated using a 3D printer (Asiga Max X, Asiga, Australia). Each HGMN is 1.8 mm in height with a base diameter of 600 µm, as shown in **Figure 2(C)**. To account for the epidermal thickness at the target insertion site on the inner arm, the hollows start 300 µm from the base [8]. This gap between the base and hollows prevents drug backflow into the tissue and exposure to air. Printing was carried out at the highest resolution, with each printed layer having a thickness of 10 µm. Figure 2(D) depicts the printed HGMN array captured using an optical microscope (VHX 7000, Keyence, Japan). The measured tip radius is 39.33 ± 2.88 µm, providing sufficient sharpness for effective skin penetration, and the measured height is 1.54 ± 0.01 mm, ensuring transdermal reach.

Characterization of HGMN

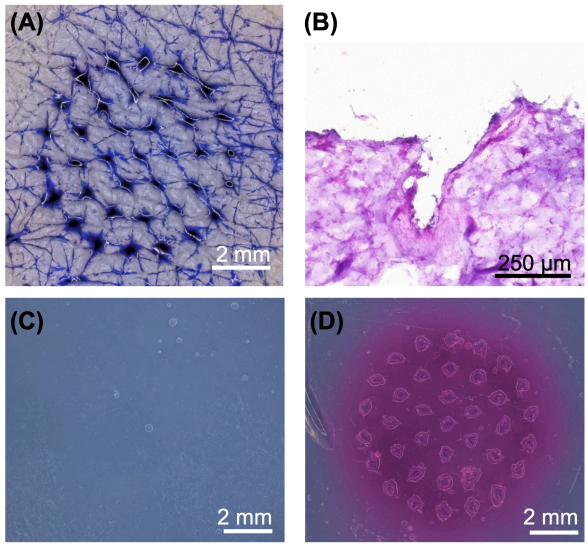

Figure 3 *(A)Porcine skin sample after insertion of microneedles loaded with trypan blue stain. (B) H&E stained section of porcine skin after insertion. Microscope images for demonstration of 3 mg/mL sulforhodamine B dye solution delivery into agarose gel (C) before and (D) after applying pressure to the pump for 30 seconds.*

To validate the performance of the HGMN, we conducted insertion into porcine tissue and agarose penetration experiments As shown in **Figure 3(A)**, a trypan blue-loaded HGMN array was inserted into the porcine tissue The HGMN array was initially pressed with finger force, and then subjected to a 200 mg weight for 2 minutes. Upon removing the HGMN array, the inserted sites filled with trypan blue were observed, confirming successful penetration. To further confirm the tissue penetration, the HGMN-inserted tissue sample was sliced into 10 µm thickness and subjected to the H&E staining. **Figure 3(B)** demonstrates successful penetration into the porcine skin. Additionally, to visualize the release after HGMN insertion, a sulforhodamine B-loaded HGMN was inserted into the agarose gel, and release was observed with the optical microscope. As shown in **Figures 3(C) and 3(D)**, the diffusion of sulforhodamine B is evident near the sites where HGMN was inserted into the agarose gel.

Characterization of Drug Stability

To achieve drug stability and maintain homogeneity, the core of the SLNPs comprised stearic acid loaded with 5-Fluo, while the shell consisted of hyaluronic acid. To investigate the performance of core-shell SLNP, the drug-carrying SLNP was compared with the blank SLNP as a control group. The charge of the outside for SLNP was measured with zeta potential. As shown in **Figure 4(A)**, the loaded and unloaded nanoparticles exhibited zeta potentials higher than -40 mV, indicating their stability. Additionally, by measuring the particle size and dispersity, the homogeneity of drug-loaded particles was evaluated. They displayed hydrodynamic diameters of 287 ± 4 and 345 ± 5 nm, respectively, with a polydispersity index lower than 20%, confirming their homogeneous size (**Figure 4(B) and 4(C)**). Drug release experiments revealed that the SLNs were capable of sustained drug release for 12 h (**Figure 4(D)**).

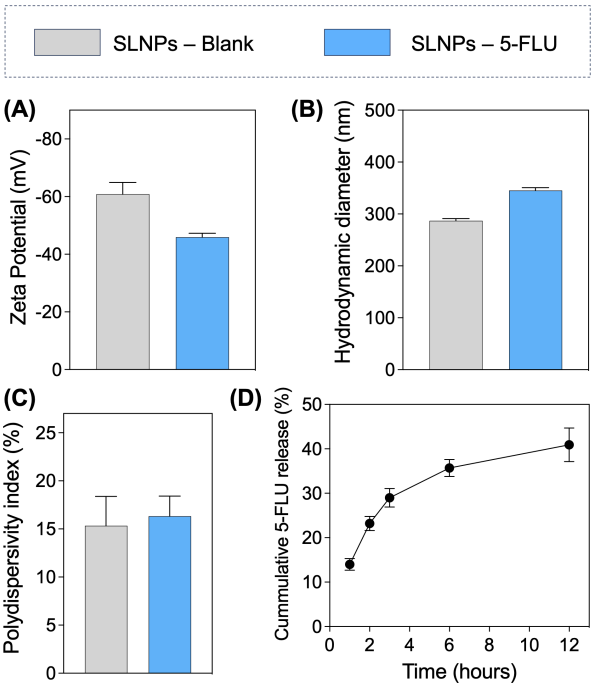

Figure 4 *(A) ζ-potential (n = 3 genuine replicates/group), (B) Hydrodynamic diameter (n = 3 genuine replicates/group)(C) polydispersity index (PDI) (n = 3 genuine replicates/group), of the different core-sheall solid lipid nanoparticles unloaded and loaded with 5-Fluorascil (5-Fluo). (D) In vitro release profiles of 5-fluorascil from solid lipid nanoparticles.*

Releasing test with HGMN array controlled by the Micropump

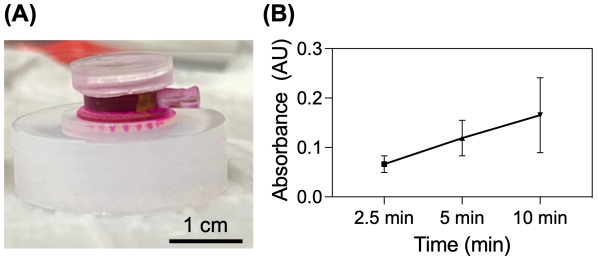

Figure 5 *(A)Photograph of releasing test with surforhodamine B dye into agarose gel. (B)Measurement of absorbance of dye released agarose at three different time points (n = 3).*

To demonstrate the controlled release of the HGMN array combined with micro pump, we conducted experiments with agarose gel as a tissue mimic. The HGMN array and reservoir were connected to the micro pump(Micro high precision peristaltic dosing pump, Gikfun, China), and the HGMN array was inserted into the agarose gel (**Figure 5 (A)**). A 150 µl volume of sulforhodamine B solution in the reservoir was dispensed into the HGMN array under the control of the micro pump. Following the filing of sulforhodamine B in the back layer of the HGMN array, the release was conducted for three different times: 2.5 min, 5 min, and 10 min. After release, by resolving the sulforhodamine B solution loaded agarose gel into the DI water, the quantitative analysis was conducted. Depending on the duration time of release, we observed an increase in the concentration of released solution into the agarose gel (**Figure 5 (B)**). This experiment confirms the feasibility of controlled drug release through the HGMN array controlled by the micro pump. Changing the quantity of drug loaded in the reservoir and the rate of pumping/loading the reservoir is expected to change the overall release profile of the drug.

CONCLUSION AND FURTHER WORK

We successfully demonstrated the HGMN array combined micro pump for the controlled release of any drugs. The complex fabrication procedures were eliminated by printing the HGMN array using the 3D printer. The performance of the printed HGMN array was demonstrated by the experiments using porcine tissue. The insertion was confirmed through the histological analysis using H&E staining, revealing the ability to penetrate the skin barrier. Furthermore, we achieved stable and homogenous drug restoration in the reservoir by loading the drug into the core-shell SLNP. Moreover, the controlled release capability through the HGMN array was illustrated by the sulforhodamine B released into the agarose gel. This highlights the potential of the HGMN array as a drug delivery system capable of controlled release. By changing the quantity of drug in the reservoir and the frequency with which the reservoir is loaded with drugs, one can achieve precise control over drug delivery profile. Moreover changing the geometry of the needles also provides another level of control of drug release.Further studies could rigorously explore various release profiles by changing the aforementioned parameters. We can also incorporate wireless control, facilitated through Bluetooth communication with smartphones to provide remotely triggered drug delivery

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CONTACT

*J.K. Public, tel: +1-617-230-4778; jihyun.kim@tufts.edu
S. Sonkusale, tel.: +1-617-627-5113; sameer.sonkusale@tufts.edu