HYDROGEL ACTUATED MICRONEEDLE (HAM) WOUND PATCH

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ABSTRACT

Chronic wounds present an expensive and time-consuming issue that affects patients each year. The challenges presented by chronic wounds stem from the drastic variations between cases, resulting in unsolvable for the long term. To address the chronic wounds and their variations, we present a Hydrogel Actuated Microneedle (HAM) wound patch. The HAM patch creates a feedback system based on the pH level of the wound state. The wound exhibits various pH levels depending on the state. It is much more effective if therapeutic agents (e.g., antimicrobial ointment, cellular growth factors) can be deployed at the most relevant dermis layer. To this end, a pH-sensitive hydrogel that responds to the present conditions of the wound can be used to pose a microneedle in a deeper or shallow region of the wound and delivers therapeutic agents. Such an approach can overcome variations from wound to wound. By having this self-positioning device with a 2.1 mm actuation range, we reduce the amount of clinical intervention within the treatment process and improve device versatility. Force and expansion studies confirm the capability of the HAM patch to push through tissue and descend into the wound. The HAM patch exceeds the average treatment depth and force of needle-based treatments.

KEYWORDS

Hydrogel, Actuator, Wound healing, Chronic wounds, Microneedle.

INTRODUCTION

Chronic wounds impact over 6.5 million individuals in the United States annually, with treatment expenditures exceeding $25 million [1], [2]. A highly efficient intrinsic host defense mechanism monitors and repairs wounds in a timely and organized manner. However, certain conditions, such as poor circulation, neuropathy, diabetes, difficulty in moving, and repeated mechanical force/stress, might interrupt the wound healing phase leaving it unresolvable for several months [2], [3]. For example, diabetic patients are more vulnerable to chronic wounds in the form of foot ulcers, leading to 75-85% of amputations [4]. As such, innovation is needed to accelerate the healing of chronic wounds stemming from an in-depth analysis of the added complexities in the healing process.

Current methods of treatment for chronic wounds follow four steps. Initially, the wound is assumed to be in the least severe state, and strategies for infection reduction and pressure alleviation, such as antibiotics and offloading, are utilized [5]. Offloading a chronic wound consists of removing mechanical stress/strain from the injured area via the application of bandages and braces. If this is unsuccessful, the wound is considered more severe and challenging to heal, and treatment advances to the next level. In this stage, medicine targets matrix metalloproteinases (MMPs) that degrade healthy tissues and physical debridement to remove unhealthy tissue [5]. Debridement is a surgical technique where the necrotic tissue is removed manually by a physician. If these techniques fail, biological methods are utilized, such as introducing collagen into the wound [6]. Finally, amputation is required if none of these methods are successful [5].

To avoid amputation, many innovations have been made to several of these techniques [7]. Qiao et al., for example, used copper-sulfide nanodots to kill drug-resistant bacteria and accelerate wound healing [8]. This process uses a bio-safe medium in order to suspend CuS nanoparticles within the wound; when activated with a laser, the nanodots will release copper ions [8]. However, like most innovative methods for chronic wound treatment, this requires an external stimulant, laser-activation, to be repeatably applied in a clinical setting. Regrettably, these present wound healing treatments frequently overlook the state of the wound.

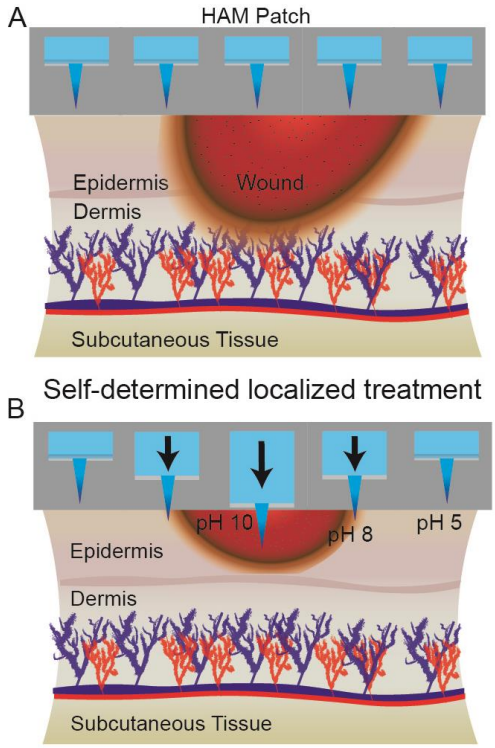

Figure 1: HAM device self-adjusting within the tissue (A) Initial application to wound (B) Microneedles responding to higher and lower pH values

To enable appropriate adjustments to the wound, we present a novel wound state-responsible patch using pH-sensitive hydrogel as a base actuator that lifts a microneedle array for a self-adjusted wound stimulator called Hydrogel Actuated Microneedle (HAM) wound patch. The HAM patch seeks to resolve the need for external clinical stimulation but utilizes the information, i.e., pH level, inside the wound. The pH of the skin is generally between 4 and 6, which is slightly acidic, providing better resistance against pathogenic bacteria. In contrast, chronic wounds raise pH up to 10 (basic), promoting bacteria growth more efficiently. The healing process moves this back to a slightly acid state, pH 5, where the wound is healed [9], [10]. As illustrated in Figure 1, the proposed HAM patch consists of a hydrogel as a base block and a microneedle array as a movable plate, constrained

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in a 3D printed flexible patch. The pH changes due to the wound state activate the hydrogel layer and swell in acidic pH or shrink in basic pH. Since the hydrogel is constrained, such chemo-mechanical actuation exerts to the opening side where the microneedle array plate is placed. This actuation poses the microneedle deeper into the chronic wound (higher pH), inhibiting bacterial activity and stimulating epithelial cells. Upon the wound recovering from the chronic condition, microneedles are retracted as is dictated by the pH level.

WORKING MECHANISMS

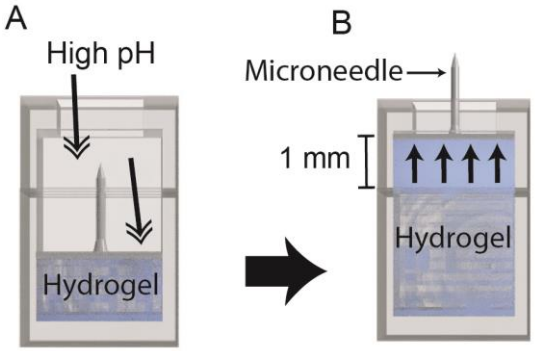

Figure 2: (A) Single cell of the HAM patch introduced to pH 10 solution, (B) resulting swelling of the hydrgoel

Figure 2 illustrates the working mechanism. The HAM patch uses two main mechanisms for operation. The first is the chemo-mechanical properties of the pH-sensitive hydrogel, and the second is the properties of constrained swelling of hydrogel. Chemically, this physical change is due to the ionic nature of the hydrogel. The hydrogel contains acidic ionic chains, which build up a charge when the external conditions contain a higher ionization [11]. This results in the lower pH values causing the increase in charge and pushing the acidic chains away from one another, hence swelling.

Once the dyed gel is formed, it becomes sensitive to environmental pH changes. In a free condition, hydrogel isosmotically swells in a basic environment or shrinks in an acidic environment. Since the swelling/shrinking is directed isotopically, all forces from this actuation are directed radially outward. To maximize the chemo-mechanical actuation and to achieve a single direction force, the hydrogel is constrained. In an ideal non-constrained isotopically swelling hydrogel, no additional stress or strain forces need to be considered. However, once an immovable blocking force is presented to one side, the stress and strain forces between the surfaces need to be considered.

Marcombe et al. reported such constrained hydrogel can be modeled as a hyper-elastic solid [12]. Several key assumptions and simplifications are made in this theory. Firstly, a hydrogel is ideal and takes the free energy to be a summation of the polymers, ionic effects, acidic groups, and entropy added in its formation [12]. In addition, the model is assumed to be electroneutral, which neglects charge interactions between the hydrogel surface and the external solution. This can be done since most hydrogel applications are on a scale larger than Debye length, which is the measure of electrostatic effects in relation to an electrolyte [12]. The concertation of the ionic species within the hydrogel, $C_{\alpha,gel}$, is the product of the ionic species in the solution, $c_{\alpha,sol,}$ and the determinate of the swelling volume F, $det\boldsymbol{F}$, Equation 1 [12].

$$C_{\alpha,gel} = c_{\alpha,sol}\, det\boldsymbol{F} \tag{1}$$

This combined with the continuum mechanics relation for stress between nominal and true, and the assumption of work summations, yields the Equation 2 [12].

$$\sigma_{ij} = \frac{NkT}{det\boldsymbol{F}}\left(F_{iK}F_{jK} - \delta_{ij}\right) - (\Pi_{sol} + \Pi_{ion})\delta_{ij} \tag{2}$$

In which σ_{ij} is the stress on the system, N represents the number of polymer chains within the network, kT is the temperature of the system, δ_{ij} is the total deformation due to the applied expansion, and Π is the difference of osmotic pressures due to the solution and the imbalance of ions. Based on Equation (1) and (2), the true stress of the hydrogel in relation to the nominal stress can describe the stress under constraints in different solutions as Equation 3 [12]. Equation 3 works as a model for the hydrogel expansion based on the ionic difference between the hydrogel and the external solution.

$$N_A K_a = c_{H^+}^{ref} \exp\left(-\frac{\gamma}{kT}\right) \tag{3}$$

Here, we used Avogadro's number, N_a, the pK_a of the solution in addition to the specific concentration of H^+ ion in the acidic chains within the hydrogel. Lastly, we used the enthalpy of the acidic dissociation from expansion, γ [12].

FABRICATION

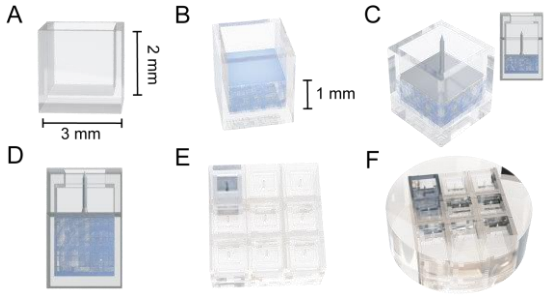

Figure 3: Fabrication of one cell of the HAM patch, (A) soft 3d printed HAM cell, (B) case is filled with 1mm thick hydrogel solution, (C) microneedle is placed on the curing hydrogel, (D) stopper application to casing, (E) Final HAM device with 9 cells, (F) HAM cells inside of circular patch.

The fabrication process is illustrated in Figure 3. First, the hydrogel was prepared by mixing acrylamide (AAm, Sigma) with methacrylic acid (mAA, Sigma) along with tetramethyl ethylenediamine (accelerator, Sigma) and N,N'-methylenebisacrylamide (crosslinker, Sigma). To better visualize the pH changes of the hydrogel, a phenol red indicator dye was added, allowing for a visible color change for ease of measurement. For a wound patch, a 3D-printed flexible patch was created consisting of an array of one or more rectangular cells (2 x 2 x 3 mm^3) (Flexible resin, Formlab 2) (Figure 3A, B). Each cell was filled with a 1mm thick hydrogel. This initial structure directed the actuation force to a moveable microneedle platform. The microneedle array was prepared using UV- light diffraction based off previous work [13]. Then, the microneedle platform was treated with γ-Methacryloxypropyltrimethoxysilane 99.04% (MPS) solution. The MPS treatment promoted the adhesion between the hydrogel and the

microneedle platform. The MPS treatment was initiated by soaking the microneedles in a solution of 10% of MPS in acetone for one hour, followed by evaporating acetone on a hot plate at 60 C for two hours. Note that such temperature was determined not to damage the microneedle. The MPS treated microneedle platform was then placed on top of the hydrogel block (Figure 3C). To retain the microneedle platform within the patch, a stopper was added (Figure 3D). This stopper included a chamber with a height of 1 mm, thus providing room for actuation. A height of 1 mm was chosen to allow the microneedle to be slightly below the stopper in its neutral state and fully extended in its swollen state. The same procedure was repeated for each cell in an array (Figure 3E). Lastly, the assembled microneedle array with hydrogel block was mounted in an easy-to-use, flexible, circular base (Figure 3F). By assembling the patch as a collection of smaller hydrogel cells on a flexible substrate, the HAM patch can adjust to the necessary depth individually as dictated by the pH level. Since each cell is acting as its own system, if one section of the wound begins to heal faster than another, the patch can react accordingly. The HAM patch prototype then underwent a pre-soak process where it was submerged in deionized water overnight. The pre-soak process allowed for the hydrogel to reach an equilibrium state at a neutral pH, ensuring the resulting actuation is caused by the appropriate pH level and not water absorption.

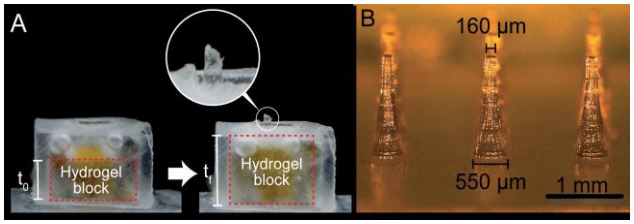

Figure 4: (A) Single HAM cell before and after presoak procedures. (B) Macro-picture of the microneedle

RESULTS

When initial equilibrium was reached the final height of the hydrogel layer is 2 mm, as seen in Figure 4. After the pre-soak, the validation of the pH-sensitive actuation of the HAM patch began by exposing it to different pH level solutions. For these tests, a pH buffer solution with pH 10 (BioPharm) was chosen to mimic the chronic wound environment. For experimental ease, the patch was inverted for all tests. Our validation procedure focuses on two aspects: force from the hydrogel actuation and height of microneedle extrusion. In order to get the maximum effects from the hydrogel, three different cell footprints were tested. Our smallest size featured a 2 mm-by-2 mm footprint, the medium size utilizes a 3mm-by-3 mm footprint, and the largest utilizes a 4 mm-by-4 mm footprint. For all three footprints, the height of the hydrogel was fixed at 2 mm tall. By testing these sizes, we optimized the dimensions of a single cell.

In order to test actuation force, a single hydrogel-microneedle cell of the HAM patch was placed in a small chamber filled with the pH 10 solution. The force from the resulting expansion was measured using a force meter (Torbal), which was placed above the HAM cell contacting the tip of the microneedle. While the HAM cell was left to expand for 90 minutes, the force was recorded simultaneously (Figure 5). The 2 mm-by-2 mm footprint of hydrogel bases exerted the highest force (262 mN), while the 4 mm-by-4 mm dimension showed almost no force even though some swelling was observed. The measured force exceeds the reported required force for skin penetration (250 mN) [14]. This skin penetration threshold is shown in a dashed line in Figure 5. However, in most cases, the HAM patch would be used on an open skin, which requires a minimal force to rip and penetrate the skin tissue.

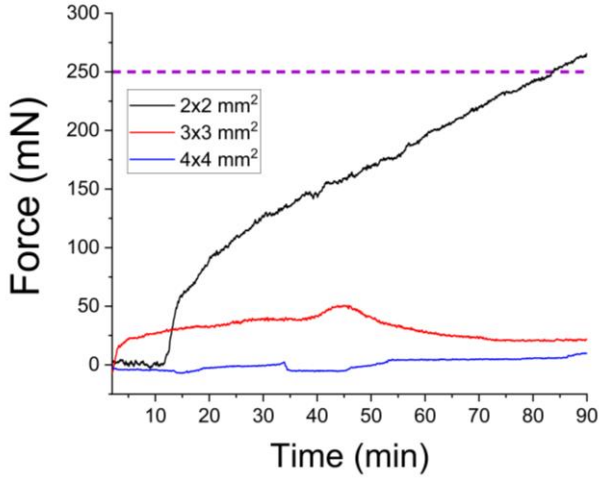

Figure 5: Force measurements for three hydrogel dimensions

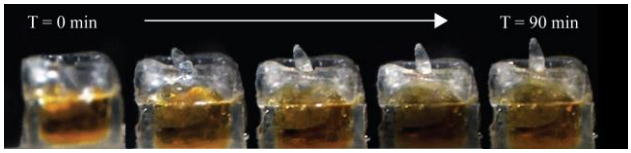

Figure 6: Example images of microneedle actuation when exposed to pH 10 environment for 90 min

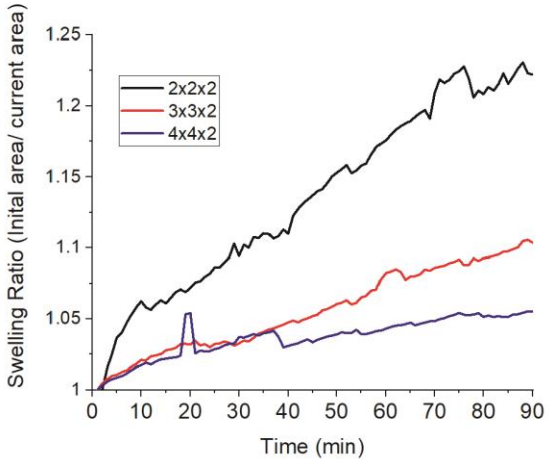

Figure 7: Swelling ratios comparison for the swelling of three hydrogels.

In addition to being able to move through tissues, the HAM patch must reach deep enough to be effective. For quantification of the HAM actuation height, an imaging trace was used. The HAM cell was photographed every 60 seconds over a 90 min span from the side of the chamber. An example of these images is shown in Figure 6. As the hydrogel expanded, the microneedle platform was lifted. The increased area from the dyed hydrogel was measured using ImageJ software.

This value was reported in terms of the swelling ratio, i.e., the ratio of the initial area over the current area. Figure 7 shows the swelling ratio results. We observed that the smallest footprint (2mm by 2mm) showed the most actuation. The overall growth translated to 2.1 mm in height, which allowed the full extrusion of the needle into the wound. Considering some of the clinical trials of needle-based wound treatment depths of 0.2 mm to 0.5 mm [15], the HAM patch with 2 mm by 2 mm cell was able to exceed the maximum depth 4-fold. Note that this maximum depth could also be controlled with a mechanical stopper, which can be customized for various applications.

Overall, we could confirm that out of three footprint dimensions (2mm-by-2mm, 3mm-by-3mm, and 4mm-by-4mm) the smallest dimension displayed sufficient force and actuation to adequately address a chronic wound. The compact size of a singular cell also allowed for more microneedles on a patch which will increase the precision of treatment.

CONCLUSION

The hydrogel actuated microneedle exhibited promising results, making it a feasible candidate in future wound healing applications. From our results, we found that the hydrogel actuation had a sufficient actuation range to allow for full penetration of the microneedle. We have also confirmed that the HAM patch is able to generate enough force to penetrate unbroken skin if needed. For future studies, we will further scale down the design, and incorporate mechanisms for drug delivery and advanced healing techniques. Using these advances the HAM patch provides a promising application, for chronic wound treatments without the need for repeated clinical intervention.

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