ADVANCING DRUG DELIVERY WITH POCKET MICRONEEDLE ACHIEVING DUAL-DRUG SYNCHRONIZATION

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ABSTRACT

This paper presents an innovative drug delivery using advanced pocket microneedle technology. The microneedle integrates two drugs: one housed inside the pocket and the other as an exterior coating. This design allows for targeted delivery of the coated drug to the skin's surface and the pocket-contained drug to the inner layers. The exterior coating, nitric oxide-polyvinylpyrrolidone (NO-PVP), exhibits antimicrobial properties, while the pocket contains niacinamide to promote cell proliferation in deeper skin layers. Fabricated using diffraction lithography, the microneedle demonstrates precise control. Successful testing on pig cadaver skin took place to validate the design, fabrication, and dual-drug application.

KEYWORDS

Pocket microneedles, diffraction lithography, transdermal drug delivery, dual drug administration, Niacinamide, nitric oxide-polyvinylpyrrolidone (NO-PVP).

INTRODUCTION

Transdermal drug delivery through microneedles has presented itself as an attractive alternative for hypodermic needle injection, given its minimally invasive nature while offering great convenience to patients for at-home microneedling [1]. Various microneedle-based drug delivery methods have been developed to satisfy various purposes and demands, including typical poke-and-patch via solid microneedle, poke-and-release dissolving microneedle, and coat-and-poke drug-coated microneedle [1]. While these three types of microneedle drug delivery methods share common features, such as ease of fabrication and use, good stability, and good manufacturability, they also share similar disadvantages including low drug loading capacity, poor drug availability and compatibility, and low drug delivery efficiency [2]. Hollow microneedle, on the other hand, has been gaining popularity due to its versatility for injecting or extracting substances as well as high molecular weight compounds with reasonable drug delivery efficiency and drug type availability [3]. However, hollow microneedle delivery is often associated with a complicated fabrication process, poor hole quality, and typically requires an external syringe device, limiting its manufacturing possibility as well as patient compliance [4].

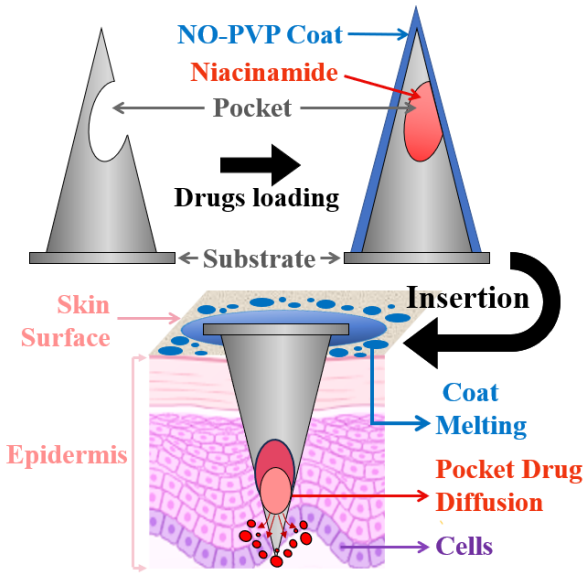

Figure 1: A conceptual drawing of the pocket microneedle applied to human skin.

To overcome the challenges mentioned above, an innovative drug delivery method, namely pocket microneedle was introduced, as described in [5]. This method highlights several promising features, including controlled drug loading capacity, precise targeting to the skin, and multi-layer drug delivery for synchronized administration of two drugs. Contrary to conventional drug delivery methods, this method allows the ability to integrate dual drug delivery mechanisms within a single applicator, thereby enhancing drug delivery efficiency and improving patient comfort. To fabricate the pocket microneedle, conventional microfabrication approaches, such as UV lithography, have encountered challenges primarily because of the 3D microneedle shape and the presence of an internal pocket. Furthermore, recent 3D printing methods, including stereolithography, have not proven suitable for achieving a smooth surface and pose difficulties when it comes to mass production.

Previously, we developed a versatile microneedle fabrication known as diffraction lithography. This method has been successfully applied to fabricate various types of microneedles, including solid, hollow, and leg-supported microneedles, as described in [6]–[9]. In this paper, we leverage this well-established method to produce three-

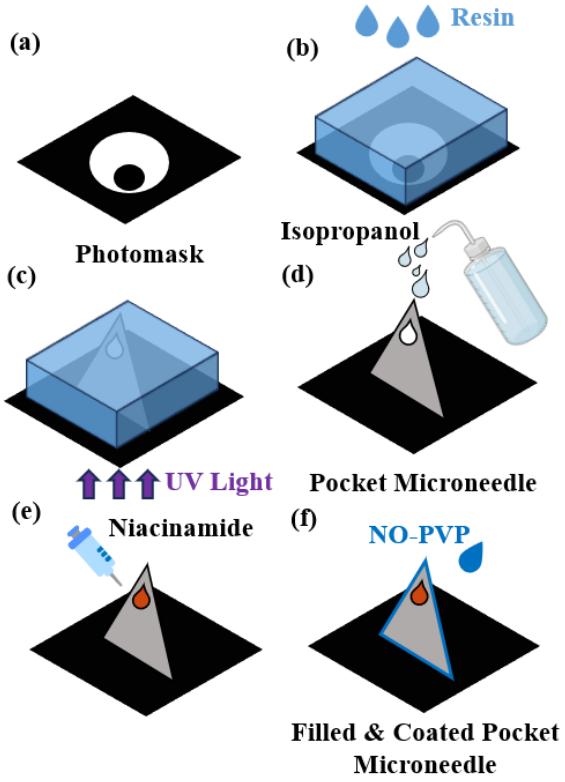

Figure 2: The fabrication process of the pocket microneedle. (a) Photomask preparation. (b) Drop-coating photopolymer resin. (c) Backside UV exposure. (d) Development in isopropanol (e) Niacinamide injected into the pocket. (f) NO-PVP drop-coated on the microneedle's surface.

dimensional (3D) pocket microneedles, as depicted in Figure 1, to enhance transdermal drug delivery. In our approach, the pocket was equipped close to the tip of the microneedle for maximizing drug delivery depth. Two types of drugs were loaded onto the pocket microneedle individually, where the first drug resided within the pocket, while the second drug was coated on the external surface of the microneedle. This design allows for the application of the externally coated drug to the skin surface, while the pocket-contained drug targets deeper skin layers for sustained treatment. For our application, the external coating utilizes nitric oxide-polyvinylpyrrolidone (NO-PVP) for its antimicrobial properties. Simultaneously, niacinamide is housed in the pocket and is renowned for its skin benefits such as enhancing the skin barrier and helping with pigmentation and skin inflammation [10].

METHOD AND FABRICATION

Figure 2 depicts the fabrication process of the 3D pocket microneedle. A photomask with a transparent outer circle and an opaque inner circle was prepared as shown in Figure 2(a). The diameters of the outer and inner circles were designed to be 250 and 150 µm, while the center of the inner circle was shifted by 25 µm to enable sharp tip and side pocket formation as described in [11]. The photomask was cleaned using acetone, methanol, and isopropanol then dried with compressed air.

The photomask was drop-coated with a biocompatible photopolymer resin (Formlabs Inc, Surgical Guide Resin)

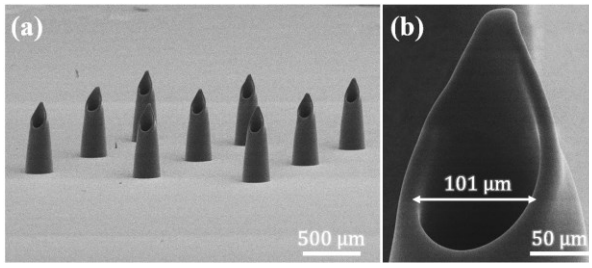

Figure 3: SEM image of a 3×3 array of pocket microneedle with diameter of 250 µm and height of 500 µm. (a) Overview of the microneedle array. (b) Zoomed-in view of the pocket microneedle.

and subjected to a backside UV exposure using a custom-made UV-LED exposure system [12] with an intensity of 5.9 mW/cm^2 for 90 sec as illustrated in Figure 2(b) and (c). The sample was dipped in a swirling isopropanol bath for 2 min then gently sprinkled with isopropanol, as shown in Figure 2(d), to remove the excess resin on the microneedle surface and partially developed the resin encapsulated inside the pocket. After drying the microneedles with compressed air, the photomask is placed on a 60 °C hotplate to form a concave profile of the pocket while eliminating isopropanol that was trapped in the pocket during the development process. The pocket microneedles were carefully dried using compressed air. A final flood UV exposure with an intensity of 80 mW/cm^2 was performed to ensure the durability and biocompatibility of the microneedles.

To utilize the dual drug delivery methods proposed, the pocket of the microneedles was loaded with niacinamide, while the surface of the microneedle was drop-coated with NO-PVP. Niacinamide mixture was prepared by mixing 1 g of niacinamide powder (Sigma Aldrich) and 0.1 g deionized (DI) water, with a drop of red color dye as an indicator. The niacinamide mixture was loaded into the microneedle's pocket using a 33-gauge needle until full as illustrated in Figure 2(e). 15 wt. % of NO-PVP solution was prepared by mixing PVP powder (Sigma Aldrich) with DI water and blue food coloring as the indicator. Then, the solution was drop-coated onto the microneedle's surface and baked at 60 °C for 5 min, assuring the drying and adherence of the coated to the surface as shown in Figure 2(f).

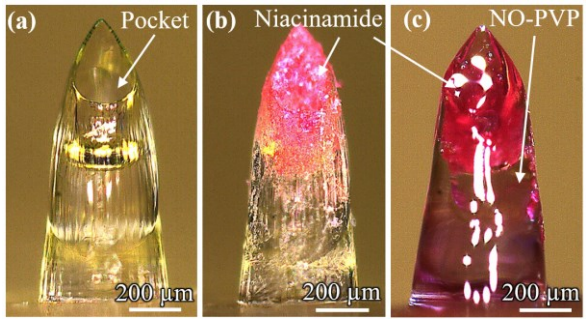

Figure 4: Optical image of a single pocket microneedle before and after niacinamide filling and NO-PVP coating. (a) Pocket microneedle. (b) Filled with niacinamide. (c) Coated with NO-PVP.

RESULTS AND DISCUSSION

Pocket Microneedles Array

The fabrication resulted in a 3×3 array of pocket microneedles as shown in Figure 3(a), showing good uniformity with 250 µm diameter and 500 µm height. Figure 3(b) shows the zoomed-in view of the pocket, with a satisfactory 101 µm opening diameter and 20 µm tip size. It is worth noting that all the presented parameters including base diameter, height, opening size, and tip size are adjustable based on the UV exposure intensity and duration.

Figure 4 shows the loading and coating results of niacinamide and NO-PVP. Figure 4(a) presents a pocket microneedle customized for this experiment, with 500 µm diameter, 1000 µm height, and 200 µm opening size. Figure 4(b) shows the pocket microneedle after being loaded with niacinamide using a 33-gauge needle and left dried naturally under room temperature. In Figure 4(c), the NO-PVP was drop-coated on the microneedle's exterior, sealing the niacinamide filling within the pocket.

Skin Penetration and Drug Diffusion

In order to validate the proposed application of pocket microneedles with a dual drug delivery functionality, a comprehensive diffusion test was conducted using the pocket microneedle as shown in Figure 4 into a gelatin as a substitute for porcine skin, allowing for visualization of drug diffusion into the deeper layers of the skin. As represented in Figure 5(a), the moment was denoted as 0 min when the microneedle was fully inserted into the gelatin. The NO-PVP that was coated on the microneedle's surface remained at the surface of the gelatin, while the niacinamide within the pocket was delivered securely deep into the gelatin, showing successful selective administration of drugs. Figure 5(b) illustrates the progressive melting of the NO-PVP in blue on the gelatin surface and the slow dispersion of niacinamide in red 30 min after the insertion. Figure 5(c) shows the complete dispersion of niacinamide in red into the gelatin 60 min after the insertion, demonstrating effective drug delivery.

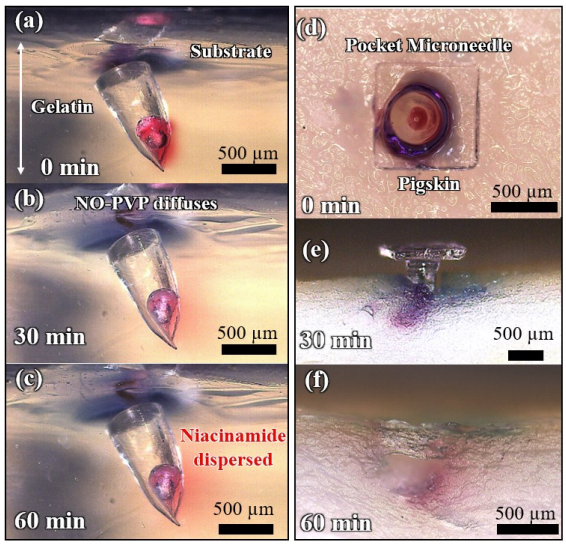

Figure 5: Insertion results of dual-drug delivery in gelatin and porcine skin. (a) 0 minute (right after insertion). (b) 30 minutes after insertion, NO-PVP diffused. (c) 60 minutes after insertion, niacinamide dispersed into gelatin. (d) 0 minute of pocket microneedle inserted into pig skin. (e) 30 minutes of diffusion. (f) 60 minutes of diffusion.

Subsequently, an insertion experiment involving an actual porcine skin, chosen for its similarity to human skin characteristics [13], was conducted to further substantiate the practicality of the fabricated pocket microneedle. In Figure 5(d), the top view of the pocket microneedle at the moment of insertion reveals the NO-PVP as a blue coating on the surface and the niacinamide in red within the pocket. Figure 5(e) shows the cross-sectional view of the pocket microneedles in the porcine skin 30 min after the insertion, with clear substantial diffusion of NO-PVP and slight diffusion of niacinamide, similar to the gelatin insertion test. Figure 5(f) shows the cross-sectional view of the porcine skin without the microneedle 60 min after the insertion, offering a detailed view of niacinamide diffusion. The results of this comprehensive test not only validate the efficacy of dual drug delivery but also verify the successful skin penetration capabilities of the pocket microneedles. This dual validation reinforces the potential of pocket microneedles as an efficient mechanism for selective and controlled dual drug delivery.

Force-Displacement Test

The durability of the pocket microneedle was subjected to a thorough analysis to validate its rigidity. The test involved a compression test with a single pre-loaded and coated pocket microneedle and a force gauge mounted to a computer-controlled linear actuator. Throughout the test, the force gauge was programmed to descend at a speed of 20 µm per sec, applying force directly at the microneedle until complete compression has occurred. Figure 6(a)

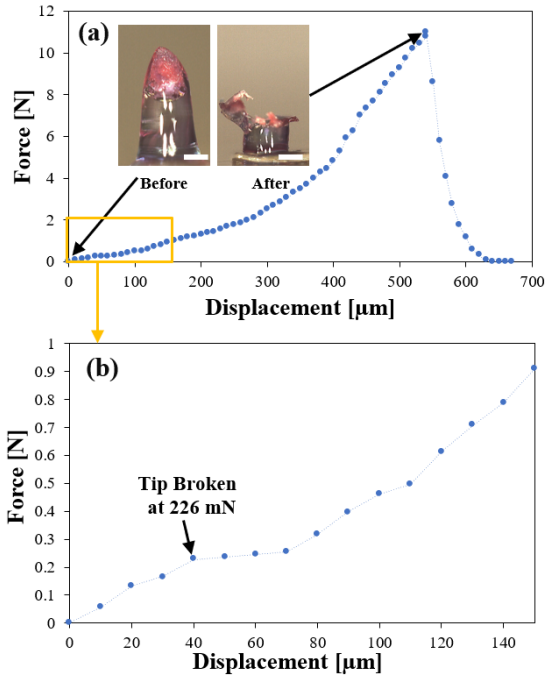

Figure 6: Force-displacement analysis of a single pocket microneedle filled with niacinamide. (a) The complete tip to base compression. (b) Close-up view focusing on tip compression. (Scale bar = 200 µm)

describes the force-displacement result of a complete tip-to-base compression of the tested microneedle, where the inset images show the images of the microneedle before and after the test. Figure 6(b) shows the close-up view of the compression results, focusing on the change in force when the tip was broken at 226 mN. This test highlights the durability of the pocket microneedle and its capacity to withstand external forces, as durability is important to predicate the ability to penetrate the human skin without causing deformation to the microneedle. This resistance guarantees the reliability of the microneedle for the duration and ensures the secure application of the drugs. This force-displacement analysis contributes insights into the microneedle's performance under external pressures, reinforcing its suitability and reliability as a dual drug delivery application [9].

CONCLUSION

In conclusion, the development of pocket microneedles introduces a new method for a dual drug delivery mechanism that reflects a new pace in drug delivery technology. By integrating niacinamide and NO-PVP, we not only provide antimicrobial properties to safeguard against infection at the insertion site but also facilitate the delivery of niacinamide into deeper skin layers, harnessing its potential for addressing issues such as hyperpigmentation. Our fabrication process, built upon diffraction lithography methods, successfully resulted in a 3×3 array of pocket microneedles with a diameter of 250 µm and height of 500 µm. After filling the microneedle with niacinamide and coated with NO-PVP, our results validate the promising drug delivery mechanism. The diffusion of both the filling and the coating in gelatin and porcine skin offers promising insights for selective and controlled drug delivery. The force-displacement test analysis further validated the durability of the pocket microneedle, as it managed to endure a compression force up to 226 mN before its deformation occurred. The versatility of the pocket microneedle design allows for the incorporation of any two drugs within a single application. This not only enhances drug delivery efficiency but also alleviates potential patient discomfort associated with multiple injections. The pocket needle method presents a practical and promising avenue for synchronized and targeted administration of therapeutic agents.

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