Morphological changes of hyaluronic acid cosmetic dissolving microneedles (DMNs) after application on the skin

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Abstract:

Dissolving microneedles (DMNs) are biodegradable polymer, such as hyaluronic acid (HA), microsized needles, designed to deliver active ingredients into the skin. They claim to be painless, to overcome the stratum corneum skin barrier and they are becoming popular in the cosmetic industry. We evaluated the morphological changes of the microneedles in a commercially available cosmetic patch, upon skin application. Two DMN patches were applied on the forearm and were removed at 30 min and 120 min, respectively. Each DMN patch was analysed under a scanning electron microscope (SEM) to observe the changes in the morphology of the needles. The SEM images revealed that the HA polymer matrix of the needles begins to weaken at the tip before the needles are dissolved completely within 120 min. Therefore, evaluation of the DMNs using SEM can provide useful insight for the claim substantiation and regulatory classification stages during the development of the patches.

Keywords: dissolving microneedles; cosmetic microneedle patch; hyaluronic acid; skin barrier.

1. Introduction

Transdermal drug delivery involves the passive diffusion of the drug into the systemic circulation via the stratum corneum; it is an appealing alternative to oral drug delivery because of the better patient compliance and avoidance of first pass metabolism, however it is limited to active ingredients with specific physicochemical properties [1, 2]. Transdermal microneedle (MN) patches enable the active ingredient to bypass the slow diffusional process across the stratum corneum's barrier and to reach directly into the deeper skin layers; MN patches are therefore suitable for the delivery of a wide range of active ingredients irrespectively of their molecular weight and their other physicochemical properties [3-9].

In recent years, the microneedle technologies developed for the pharmaceutical industry have been adopted by the cosmetic industry for the delivery of active ingredients into the deeper skin layers [10-18]. Dissolving microneedles (DMNs) offer a safe and convenient option for consumers by using a single-use biodegradable hyaluronic acid polymer matrix with encapsulated actives to temporarily puncture the skin. During dissolution of the needles the active compound is released into the skin via micro-channels for increased efficacy without generating biohazardous waste. These properties have led to DMNs being effective for the delivery into the skin of cosmetic ingredients such as ascorbic acid, adenosine and retinyl retinoate for wrinkle improvement, and 4-n-butylresorcinol, melatonin, arbutin, niacinamide and tranexamic acid for depigmentation plus horse oil for skin barrier restoration and moisturisation [13-18]. In cosmetic preparations the needles vary

in length, shape, composition, and the number of needles per array. Additionally, the patch size and shape are designed depending on the area of application and required cosmetic function; DMNs for blemishes are small and circular aimed to cover one pimple at a time whereas wrinkle patches are larger and can contain over 100 DMNs to cover a larger area of skin. The benefits of using a DMN patch for blemishes is that typical hydrocolloid patches are not recommended to be used in the presence of anaerobic bacteria. Spots which are at the very surface are accepted as the hydrocolloid material draws out the exudate and thus reducing inflammation. However, deeper rooted, early formed blemishes benefit from DMN which deliver actives such as salicylic acid and niacinamide direct to the site of infection.

The primary regulation management of cosmetics within the U.S. is the Federal Food, Drug and Cosmetic Act (FD&C Act) and the Fair Packaging and Labelling Act (FPLA) which controls the compliance criteria and the principles for labelling of cosmetics and sustainability claims provided by the Food and Drug Administration (FDA). As per the FD&C the definition of a cosmetic product is "*articles intended to be rubbed poured, sprinkles, or sprayed on, introduced into, or otherwise applied to the human body*" [19]. Therefore, under this regulation the cosmetic can generate a "physical" and not "physiological" function. Terminology and claims can determine how a product is regulated, therefore, if the MN patch claims to treat or affect the structure of the human body it would be classified a drug. Under the UK and European legislation "*a 'cosmetic product' means a substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips, and external genital organs)*" [20]. In the UK the Medicines and Healthcare products Regulation (MHRA) classifies products on a case-by-case basis. Hydrocolloid patches which contain no active ingredients but do make medical claims which relate to the physical actions of the hydrocolloid patch (e.g., protective barrier) would usually be considered a medical device. Similarly, a pre-loaded/coated microneedle patch would require consideration as whether there is an intended medical purpose for the product, the ingredients and function of the ingredients and whether the overall activity of the product is primarily accomplished by the patch or the delivered ingredient. In such cases where a product could not be a medicinal product, medical device, or cosmetic product, it would be likely to fall under the General Product Safety Regulations. Therefore, in the UK both MN and hydrocolloid patches are likely to meet the requirements of a borderline product, meaning that the regulatory classification of these sorts of products would have to be determined individually, considering the available information about the specific product in question. [21]

The aim of our study was to investigate the changing morphology of the microneedles of a commercially available cosmetic patch during application into the skin.

2. Materials & Methods

2.1 Materials

A pack of commercially available cosmetic DMN patches was purchased from CultBeauty.com. The DMNs were prefabricated on a circular hydrocolloid patch measuring 16mm in diameter. The adhesive ring measured 3mm and the central array measured 10mm with 25 DMNs in rows of two, four and six. The material of the moulded microneedles was hyaluronic acid hydrogel which also acted as the vehicle for several low molecular weight actives.

2.2 Methods

2.2.1 Skin application of the DMN patches

Self-application of the commercially available cosmetic DMN patch on healthy skin was carried out by the researcher as follows. The skin on the dorsal side of each forearm was thoroughly cleansed with a mild detergent and allowed to dry for an hour. A DMN patch was then applied onto each forearm with thumb force. After t= 30 min, one DMN patch was detached from the skin and examined using Scanning Electron Microscopy (SEM) as described in 2.2.2. The remaining DMN patch was detached from the skin and examined at t= 120 min.

2.2.2 Scanning Electron Microscopy (SEM)

A scanning electron microscope (SEM) was used for the study of the DMN patches at different time intervals (t=0, t=30 min and t = 120 min) to assess the morphology of the dissolving microneedles focusing on their length and tip geometry. A 25mm carbon tab was adhered to a 25 mm aluminium disk. Each DMN patch was placed onto the carbon tab and a thin layer of gold and palladium (Au/Pd) was applied for 108s at 30-40mA/mbar in the sputter coater forming a thickness of 5-10nm. Once coated, the aluminium disk was placed within the Hitachi S3000-N SEM and a vacuum pressure of >1Pa was created. An accelerating voltage was applied, and the filament saturation was increased to ~50mA. SEM images of the needles at different angles and magnifications (25x – 300x) were subsequently recorded.

3. Results & Discussion

The morphology of the HA microneedles is fundamental to the efficacy of the DMN patch. The needle length must be considered as it can affect the depth of penetration and release of the active ingredients into the skin, which can then have implications on the Regulatory classification of the DMN patch.

Before application on the skin, the microneedle surface was smooth and formed an irregular cone-shaped base and cylindrical tip. Viewing from above, the array appeared to have hollow needles with a small opening at the apex as shown in Figures 1a – c; however, a side view shows that the needles are not hollow but have a blunt tip (Figure 1f)

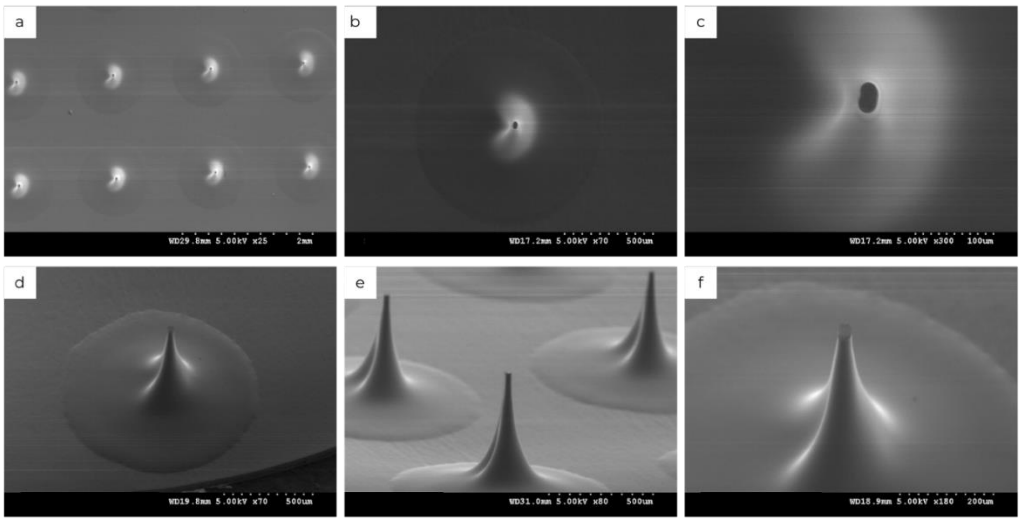

Figure 1. **a**. Microneedle array; **b**. Single DMN from above; **c**. Single DMN tip; **d**. Side view of the single DMN; **e**. Side view of the microneedle array; **f**. Side view of the single DMN tip.

The height of the microneedles was inspected before application (t = 0 min) (Figure 2a, 2d, 2f), after half an hour (t = 30 min) (Figure 2b, 2e) and after two hours (t = 120 min) (Figure 2c) of skin penetration. The average length of the DMN before insertion was 513.2 ± 27.4 µm (n = 5) as shown in Figure 2d; considering that the total thickness of the epidermis on the dorsal forearm is approximately 75 µm [22], we can deduce that the microneedles reached well into the dermis. Piercing through the dermis could cause a slight discomfort because of the presence of nerves, and it would also enable the prompt uptake of the active ingredients into the systemic circulation which should be considered during the regulatory classification of the DMN patch.

After 30 min the length of the microneedles measured 382 ± 56.1 µm (Figure 2e). After 120 min (Figure 2c) the microneedles had fully dissolved. Therefore, the microneedles fully perforated the skin, dissolved, and released the active ingredients within two hours.

It can be observed that after 30 minutes the base of all the needles remained intact and the tips appeared to show less stability by curving inwards (Figure 2b, Figure 3), however, some were shown to have complete tip loss. Additionally, some needles on the perimeter had noticeably more degradation, with the tip of the needle completely dissolved.

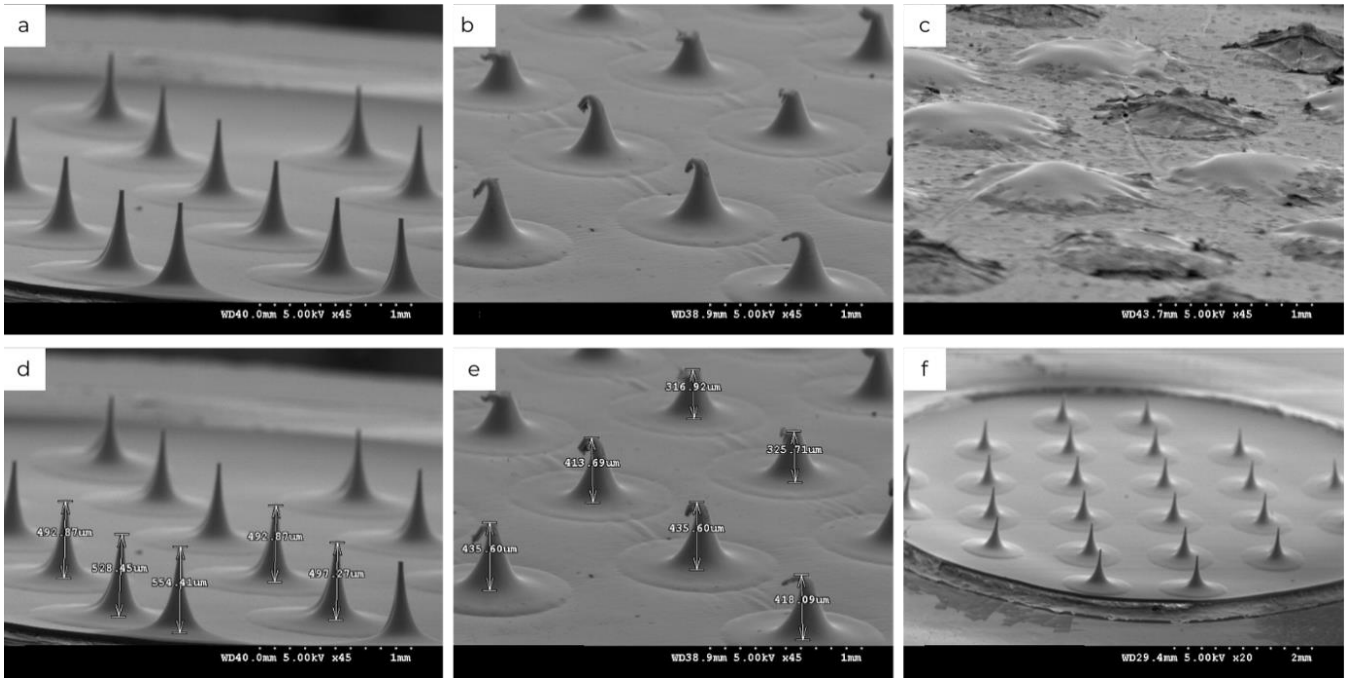

Figure 2. **a.** Dissolving cosmetic microneedles before application on the skin; **b**. upon thumb force application on the skin of the forearm the DMNs were partially dissolved after 30 minutes; **c** after 120 min the DMNs were completely dissolved; **d.** measuring the height of the DMN needles; **e** partially dissolved microneedles after 30 min with height measurements; **f**. circular DMN array with adhesive border.

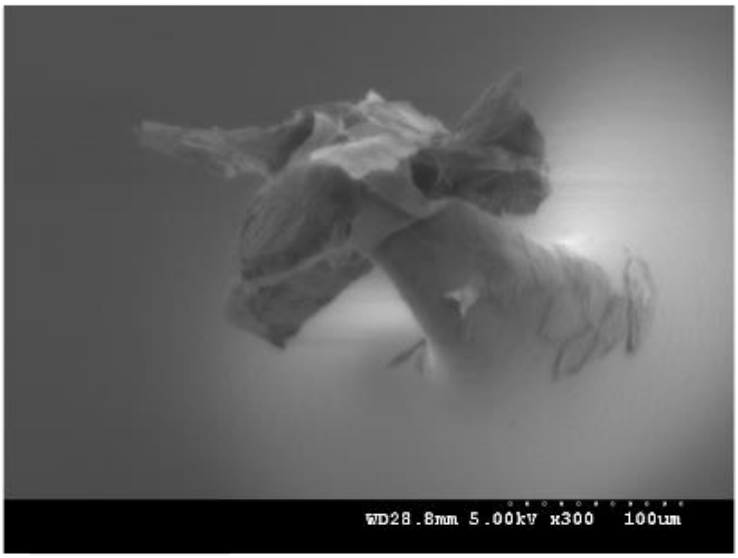

Figure 3. Morphological changes of a single DMN needle tip after 30 minutes application in the skin.

5. Conclusion

Study of the morphological changes of DMN cosmetic patches revealed that the needles were completely dissolved within 2 hours after application. The SEM technique can therefore provide useful insight on the structural changes of the microneedles at the quality control and/or claim substantiation stages of the DMN patches' development.

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