

FACILITATING TRANSDERMAL DELIVERY USING A ONE-STEP HYDROGEL FORMING MICRONEEDLE DEVICE: A CONCEPT STUDY

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Introduction

Hydrogel-forming microneedles (MNs) consist of drug-free, micron scale polymeric needles situated in perpendicular orientation on a base plate to which a separate drug containing reservoir is attached.¹ In its current form, this MN device requires the addition of water (10 μ L) prior to skin insertion both *in vitro* and *in vivo* to permit the adhesion of the drug containing reservoir to the MN array. Evidently, this creates a two-step application process which has the potential to reduce the likelihood of acceptance from both healthcare professionals and patients. For this reason, this concept study aimed to develop an applicator which can be used to insert hydrogel-forming MNs into the skin in a one-step process.

By using a water filled reservoir situated on top of a drug containing lyophilised wafer as shown in **Figure 1**, it is envisaged that upon manual thumb pressure the reservoir will burst, releasing its contents to permit the adhesion between the MN and the wafer. It is also hypothesised that despite the additional layers on top of the MN, needle insertion into the skin will not be affected. To determine how the additional water volume affects skin permeation *in vitro*, FITC-dextran 10 kDa and fluorescein sodium were used as model drug compounds.

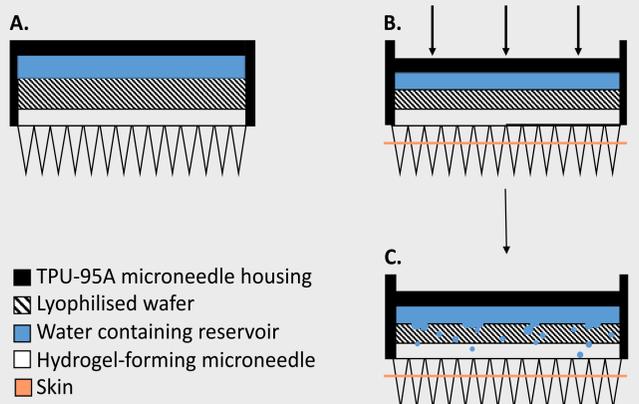


Figure 1. Schematic representation of a one-step hydrogel-forming MN insertion procedure.

Materials and Methods

Manufacture of a 3D printed MN applicator

The MN applicator was designed using a computer-aided design (CAD) software and printed with an Ultimaker3 3D printer (Ultimaker, Geldermalsen, The Netherlands) with Cura[®] software (**Figure 2**). Using one 0.4 mm nozzle on the Ultimaker3 system, TPU 95A was extruded with a print speed of 25 mm/sec and a print temperature of 215 $^{\circ}$ C. The infill layer thickness was 0.1 mm.

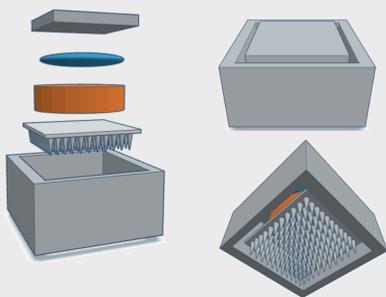


Figure 2. MN applicator concept design.

Fabrication of Parafilm[®] M water containing reservoirs

Parafilm[®] M reservoirs (PR) were produced using a heat-sealing method (**Figure 3**). A defined volume of water was dispensed into the single Parafilm[®] M pouches with the top opening then folded over and heat-sealed. % water release was then determined following the application of a 32 N force.

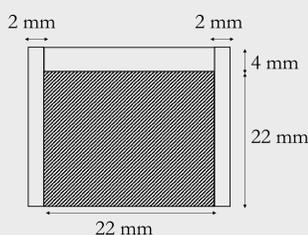


Figure 3. Schematic diagram of Parafilm[®] M and polyethylene water filled reservoirs, with the shaded region representing the water filled compartment.

Insertion of hydrogel-forming MNs into a polymeric film using a one step method

Hydrogel-forming MN arrays composed of an aqueous blend of 20% w/w Gantrez[®] S-97, 7.5% w/w PEG 10,000 and 3% w/w Na₂CO₃ with needle density 11 x 11 and 600 μ m in height, were inserted into 8 layers of Parafilm[®] M using a TA.XT Texture Analyser in compression mode. For comparison, three separate setups were used, namely 1) MN alone, 2) MN with drug containing layer and 3) PR design (MN + drug layer + water reservoir + applicator). Needle insertion was assessed by examining the holes created in each layer under a light microscope.

In vitro permeation using a one-step MN application process

FITC-dextran 10 kDa and fluorescein sodium permeation through dermatomed (350 μ m) neonatal porcine skin was quantified using modified Franz diffusion cells over a 24 hr period. Reservoirs containing 200 μ L and 600 μ L of water were tested and compared to the traditional approach which involved the addition of 10 μ L of water. Samples were analysed using fluorescence spectroscopy.

Results

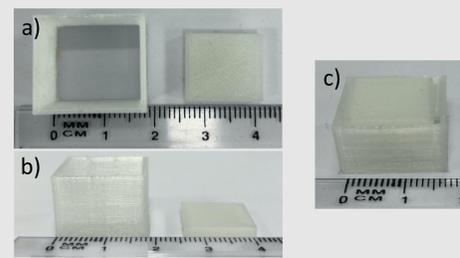


Figure 4. a) Images of 3D printed TPU 95a MN housing and lid a) top view & b) side view. c) Complete PR design containing a hydrogel-forming MN array, lyophilised drug containing wafer and Parafilm[®] M water reservoir.

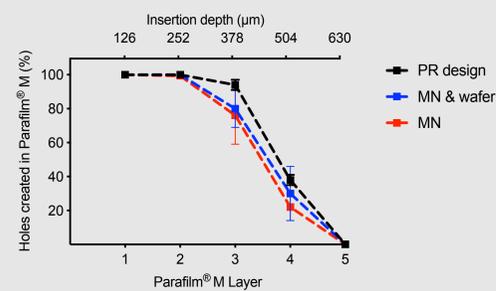


Figure 5. Percentage needle insertion and penetration depth into 8 layers of Parafilm[®] M for 600 μ m 11x11 MNs using 3 different setups into 8 layers of Parafilm[®] M following application of a 32 N force for 30 secs. This included MN alone, MN and wafer and PR design.

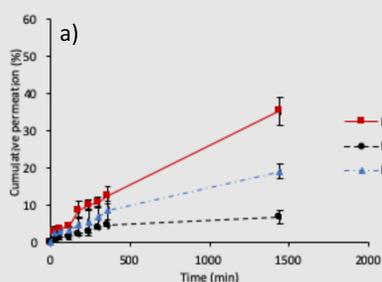


Figure 7. *In vitro* cumulative permeation profile of a) FITC-dextran 10 kDa and b) fluorescein sodium across neonatal porcine skin following a one-step application method using PR 200 and PR 600 reservoirs. The traditional approach (10 μ L of water) was used as the control (Means \pm SD, $n = 3$)

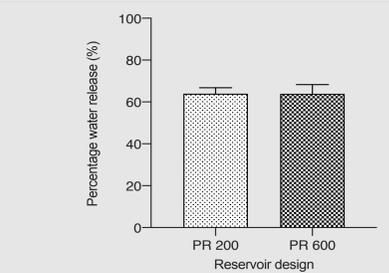


Figure 5. % water release for 200 μ L (PR 200) and 600 μ L (PR 600) reservoirs following application of a 32 N force for 30 secs, equivalent to 63.92 \pm 2.95% and 63.86 \pm 4.45% respectively.

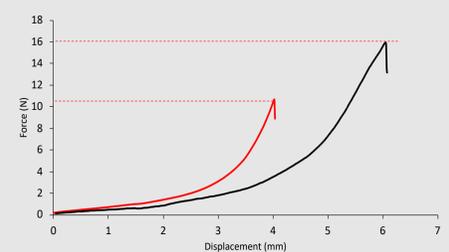


Figure 6. Force displacement graph showing the reservoir fracture point for PR 200 (18.18 \pm 1.83 N) [black line] and PR 600 (12.41 \pm 1.91 N) [red line].

Discussion and Conclusion

With the end user at the forefront of this study, a 3D printed MN housing was designed to permit a one-step MN application process. This concept design had two key aspects in mind, namely the insertion of a complete hydrogel-forming MN into an artificial skin membrane, and the potential drug permeation enhancement through the release of water immediately upon insertion. Importantly, as shown in **Figure 5**, in layer 4, representing an insertion depth of 504 μ m, no significant difference in needle insertion was observed between all three setups ($p > 0.05$). This confirms that the MN can penetrate into the rich microvascular network contained within the dermal layer of the skin when the applicator is used.

Using FITC-dextran and fluorescein sodium as model compounds, it was observed that the traditional approach resulted in a significantly greater permeation after 24 hrs for both compounds when compared to PR 200 ($p < 0.05$) and PR 600 ($p < 0.05$) *in vitro* (**Figure 7 a-b**). Although PR 600 did reduce the dissolution time of the lyophilised wafer containing the model compound, it was found that the increased volume of water resulted in a greater degree of MN swelling, ultimately causing the needles to swell out of the skin. That said, the small diameter of the donor compartment of the Franz cell apparatus may be a limiting factor and as a result, complete needle insertion may be maintained in an *in vivo* setup.

Ultimately, we have shown for the first time that a MN applicator device can be used to correctly insert a complete hydrogel-forming MN system into the skin. However, increasing the volume of water released during insertion did not significantly enhance permeation as previously thought. Additional work is now required to determine the optimum volume of water to facilitate drug permeation from this one-step applicator device.

References

1. Donnelly, R.F. *et al.* Drug Deliv. 2010; 17: 187-207