3D PRINTED HOLLOW MICRONEEDLES FOR TRANSDERMAL INSULIN DELIVERY

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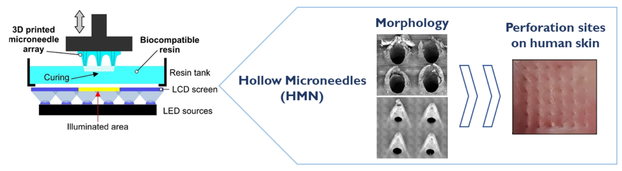
Introduction

Microneedles (MN) are miniature devices of a maximum length of 1000 μm, capable of perforating painlessly stratum corneum and releasing their active content in the skin layers beneath. The significance of MNs lies on the fact that they have the potential to substitute the fear inducing injections, while avoiding first pass effect or other possibly unwished metabolic changes of the oral administration[1]. In the current study 3D printed microneedles were fabricated by means of liquid crystal display (LCD) vat polymerization 3D printing technology for the transdermal delivery of human insulin in vitro[2].



Materials and Methods

HMN (hollow microneedles) arrays (6 × 6) were designed with two different geometries; namely "curved pyramid" and "syringe-like" using SolidWorks CAD software (Dassault Systèmes, SolidWorks Corporation, Waltham, MA, USA). Height was set to 1000 μm, while interspacing to 2000 μm (center to center distance). The whole patch was a 15 × 15 mm square surface. 3D-printing was conducted with Phrozen Shuffle 2018 3Dprinter, by means of photopolymerisation. Resin NextDent Ortho Rigid, a biocompatible resin (Class IIa) was used as printing material and final printing parameters were adjusted with ChiTuBox 64 slicing software. Permeation studies were conducted using vertical Franz diffusion cells and human insulin. Skin samples were heated for 2 min at 60 °C and epidermis layers were removed using blunt forceps. Epidermis was fixed with 10% formaldehyde solution for 10 min. Subsequently, epidermis samples were placed in alcoholic solutions of increasing concentrations namely 50, 70, 96 and 100%, for 30 min in each case. Upon their dehydration skin samples attached on metal stubs using carbon tape and further visualized by means of SEM.

Results

Fabrication and characterization of microneedles

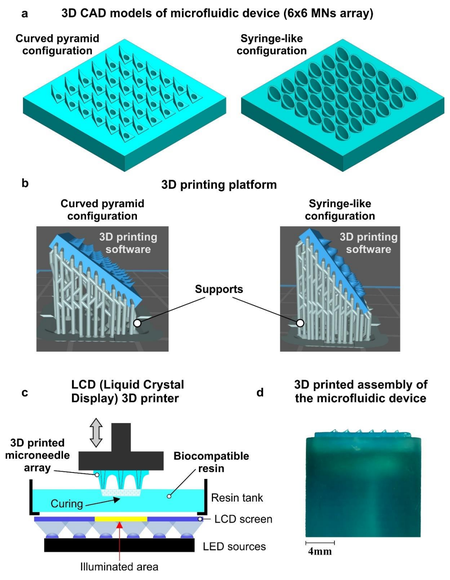


Figure 1. a) 3D CAD models of microfluidic device (b) 3D platforms (curved pyramid and syringe-like configurations), (c) Schematic representation of the vat polymerization 3D printer for the fabrication of the HMN arrays and reservoirs and (d) the 3D printed microneedle arrays fitted in a reservoir adapter suitable for drug administration

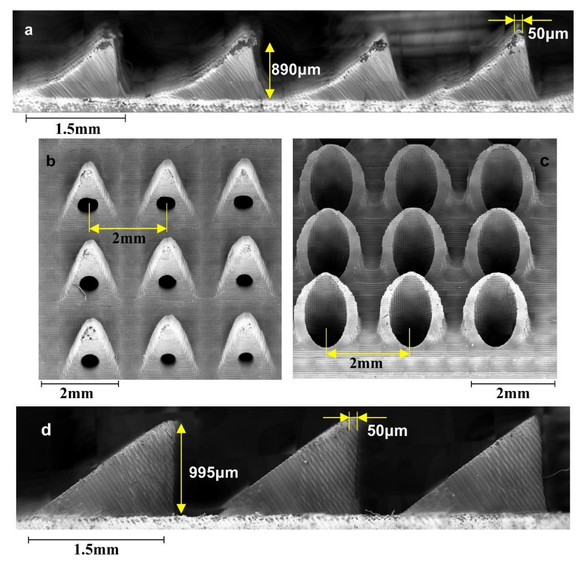


Figure 2. SEM micrographs: (a), (b) 3D printed curved pyramid and (c), (d) 3D printed syringe -like HMN arrays.

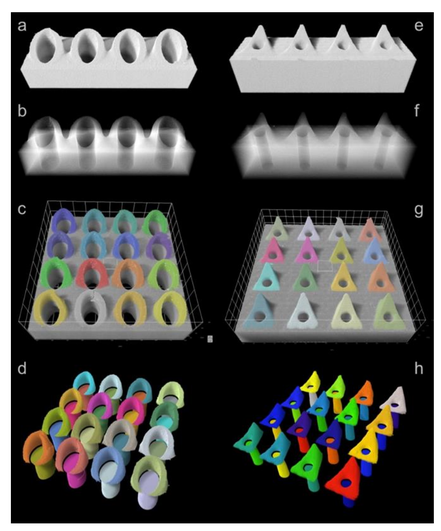


Figure 3. X-ray μCT of curved pyramid, syringe-like HMNs and their microchannels. Volumetric (a), (e) and semitransparent (b), (f) virtual section of a single needle row showing the needle structure and the lumen with respect to the needle. Sub-panels (c), (d) and (g), (h) show the segmented individual needles (c), (g) and the needle / lumen models (d), (h) used for the quantitative analysis.

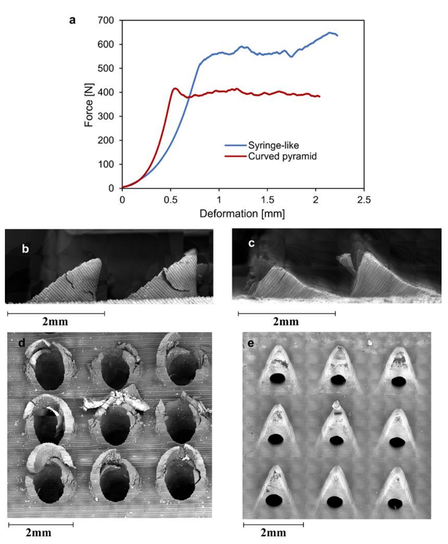


Figure 4. (a) Failure tests demonstrating force-displacement experimental data, (b), (c), (d) and (d) SEM imaging of the curved pyramid and syringe-like HMN configuration after compression test.

Permeation studies

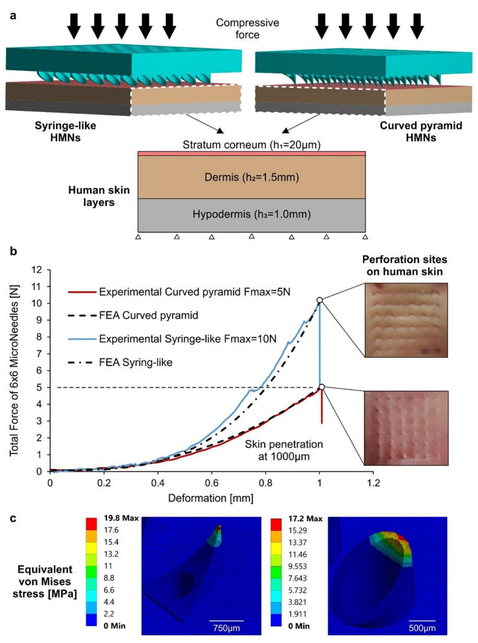


Figure 4. Penetration tests using the curved pyramid and syringe-like HMNs: (a) schematic representation of FEA simulation, (b) insertion force-deformation curve-fitted by FEA along with the perforation sites on human skin and (c) stress distribution of curved pyramid and syringe-like HMNs at the last step of the simulation of skin penetration using FEA.

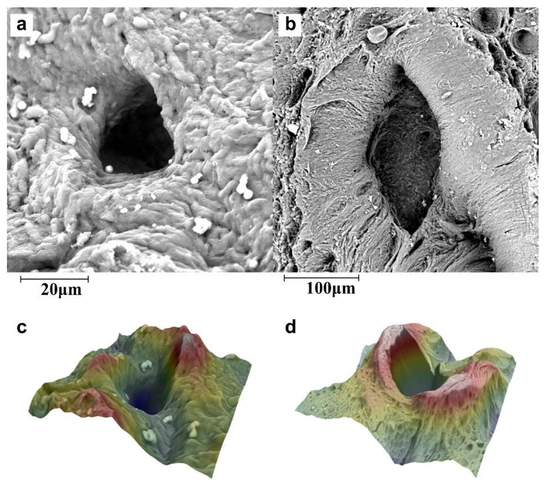


Figure 5. SEM imaging of microneedle created perforation sites for (a) curved pyramid HMNs (b) syringe-like HMNs and 3D roughness reconstruction of perforation sites for (c) curved pyramid HMNs (d) syringe-like HMNs.

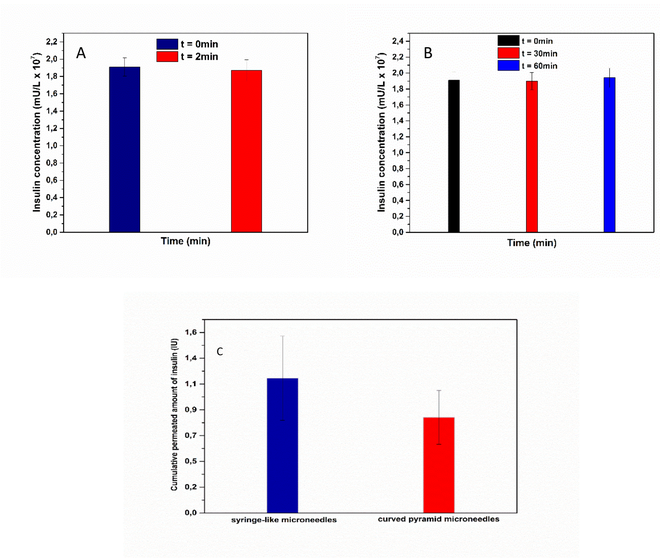


Figure 6. (a) Binding studies of insulin to surfactant coated microneedles (n=3), (b) stability studies of insulin at 37°C (n=3) and (c) cumulative amount of insulin permeating human skin after HMN treatment.

Conclusion

In the current study the structural features of two different 3D printed 6x6 HMN geometries were assessed. Non-destructive 3D (volumetric) imaging by means of μCT demonstrated that the 3D printing method used in this study allows for high consistency and reproducibility with respect to needles' geometric characteristics. Diffusion studies demonstrated that syringe-like HMNs were more effective upon insulin administration compared with curved pyramid ones. Although syringe-like geometry penetrates skin at higher insertion force, it is probably more suitable for macromolecular drug delivery which might be attributed to the geometrical characteristics of the microneedles.

References

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2. Xenikakis, I, Tsongas K, Emmanouil K. Tzimtzimis, E.K., Katsamenis O.L., Demiri E, Constantinos K. Zacharis, C.K., Georgiou, D., Kalogianni, E.P., Tzetzis, D., Fatouros, D.G. Transdermal delivery of insulin across human skin in vitro with 3D printed hollow microneedles. J Drug Deliv. Sci. Techn. (2021)

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