APPLICATION OF 3D PRINTING TO MICRONEEDLE-MEDIATED DRUG DELIVERY AND INTERSTITIAL FLUID EXTRACTION

Tech Session 4: Additive Manufacturing
Thursday 14th July 2022

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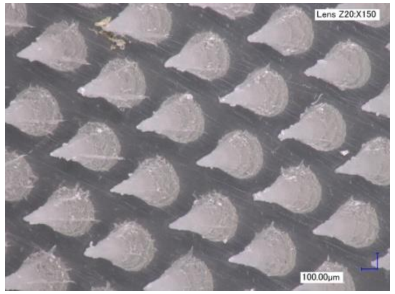
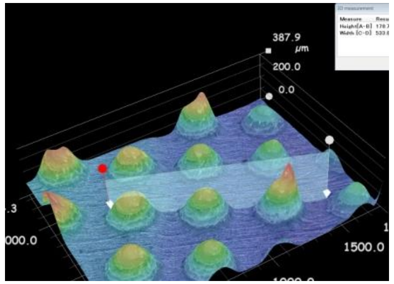
OVERVIEW

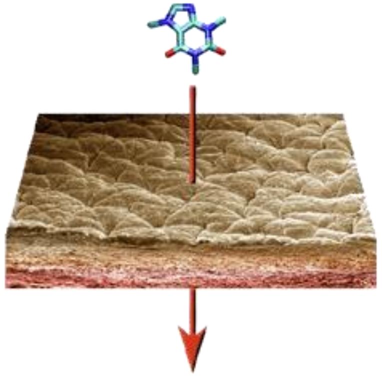




- The role of drug delivery in recovery of healthcare systems
- Change of mind set to consider transdermal delivery of high doses and controlled release after patch removal
- Design & manufacture considerations
- 3D printing as a tool in microneedle manufacture
- Application to drug delivery and patient diagnosis/monitoring
- Industrial translation and next steps

A ROLE FOR DRUG DELIVERY IN PANDEMIC RECOVERY?

- The COVID-19 pandemic has had a profound, detrimental, effect on healthcare systems worldwide
- Substantial backlogs in diagnosis and treatment
- Routine injectable drugs still require attendance at a healthcare setting
- Ever-increasing prevalence of injectable medicines
- At-home administration would free up healthcare providers and reduce risk of COVID spread
- Considerable issues with needle phobia and inappropriate reuse and unsafe disposal
- Oral administration of most injectable drugs is not feasible or extremely inefficient



Transdermal Drug Delivery

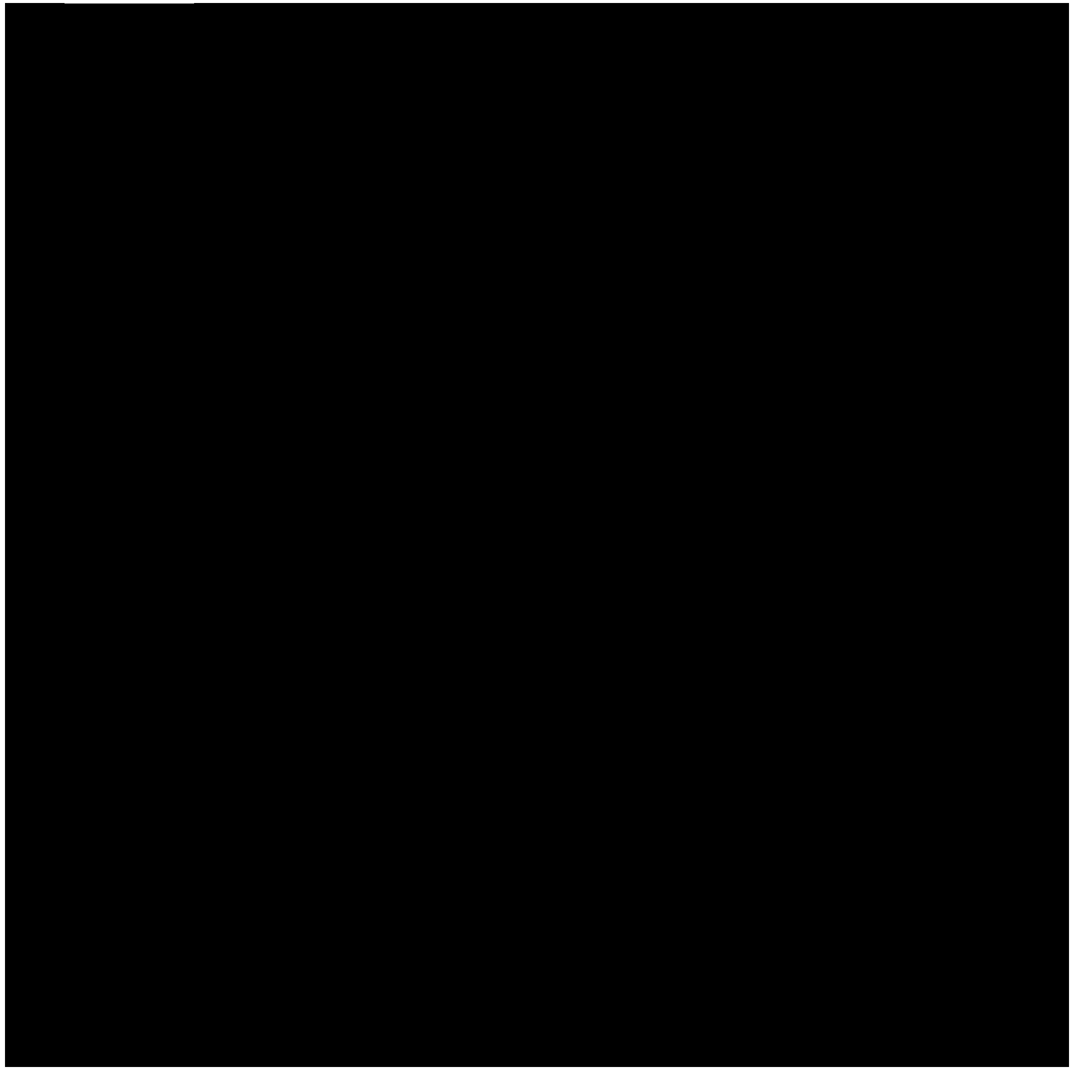
- The worldwide transdermal patch market approaches $32 billion, yet is based on less than 20 drugs.

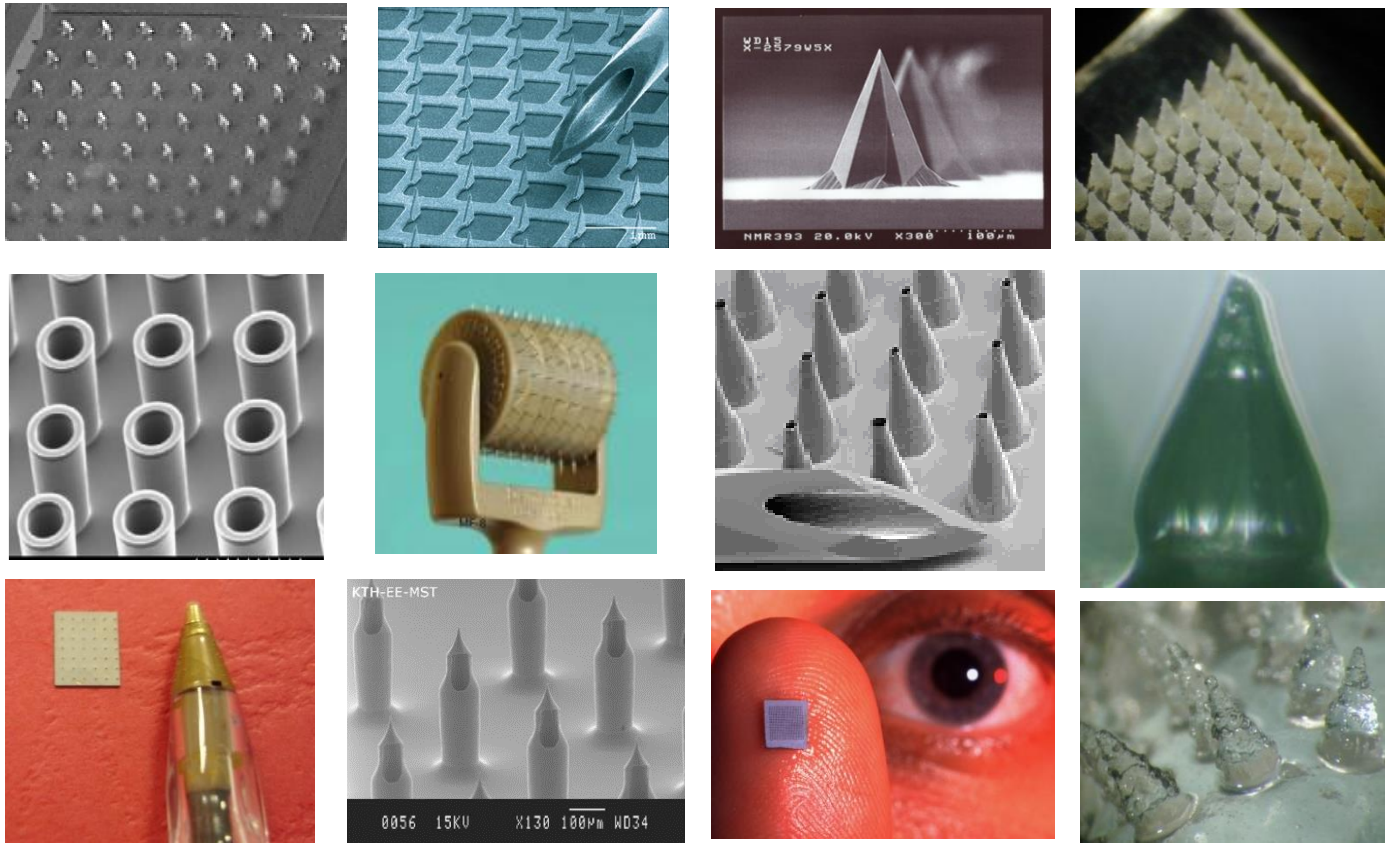
- Transdermal drug delivery is currently limited to drug substances possessing very specific physicochemical properties, namely:

- Molecular mass < 600 Da
- Adequate solubility in both oil and water
- High SC:vehicle partition coefficient
- Low melting point, correlating with good solubility

- **Clearly, many drugs which would benefit from transdermal administration do not possess these characteristics**
- **Penetration enhancers, pro-drugs, ion-pairs have limited enhancement capacity, while iontophoresis, sonophoresis, electroporation and jet-injection have all had limited impact**

MICRONEEDLE DELIVERY SYSTEMS



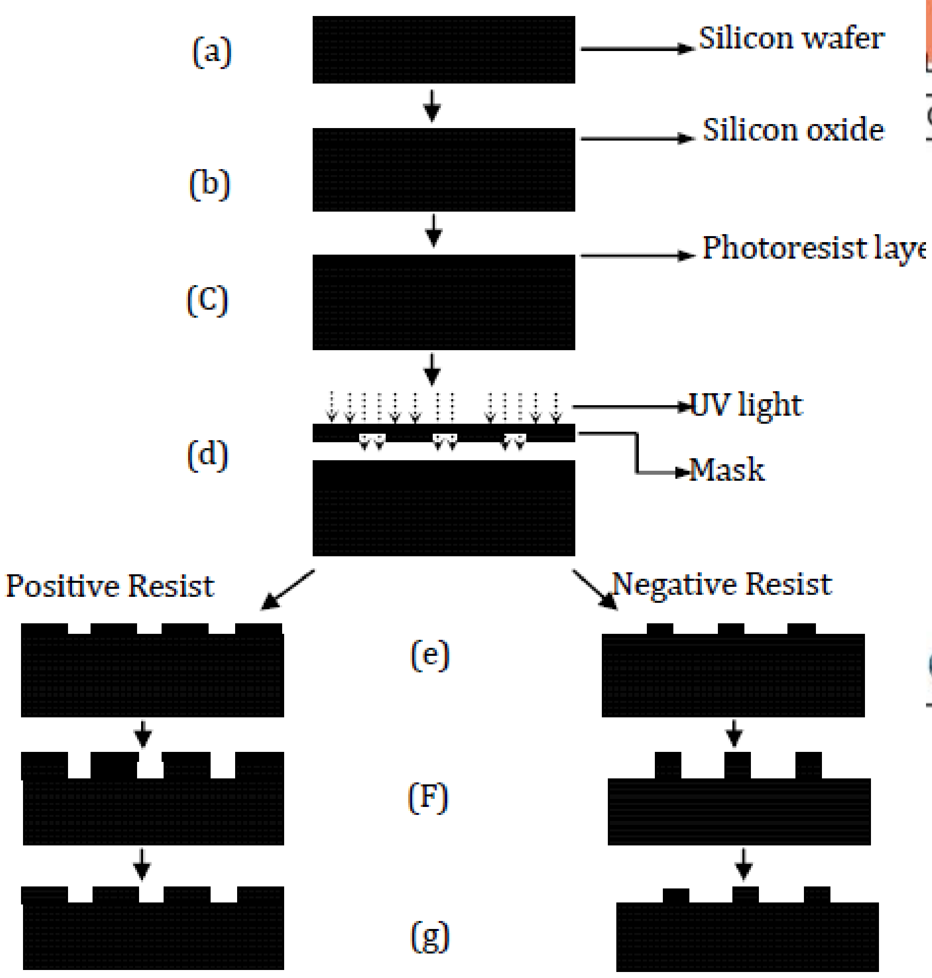


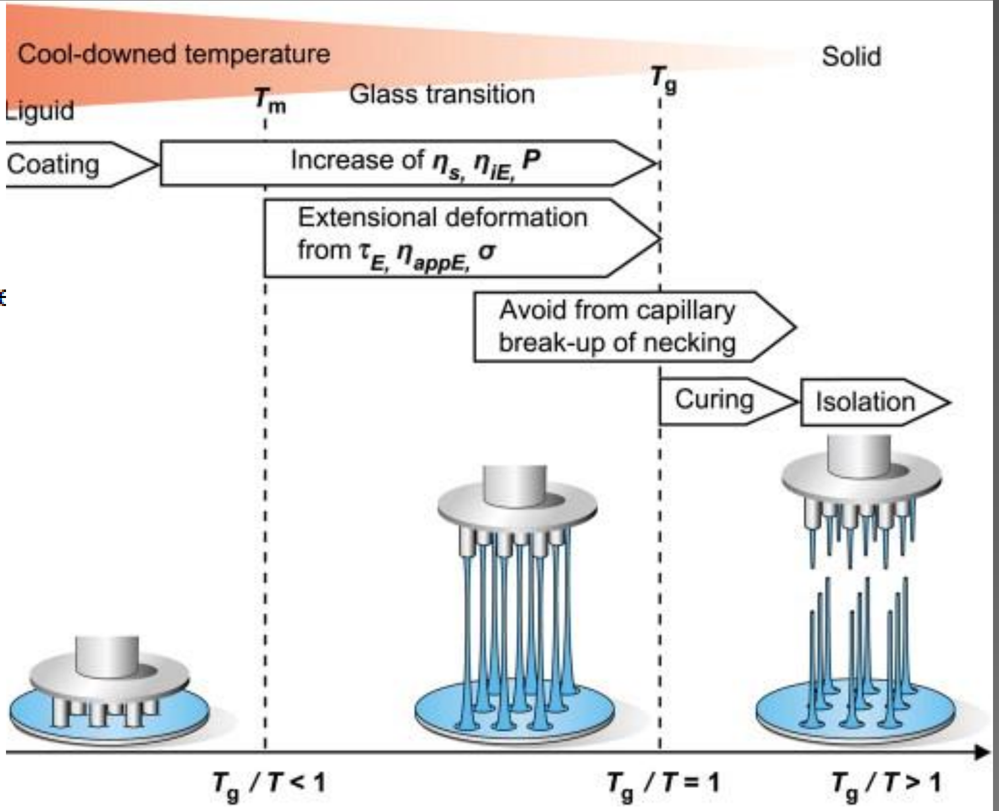
- Micron-scale (< 1mm)
- Painless
- No bleeding

- Typically small patch sizes
- Usually low doses
- Vaccine delivery
- <u>**Potential for drug delivery?**</u>

Michelson
DIAGNOSTICS

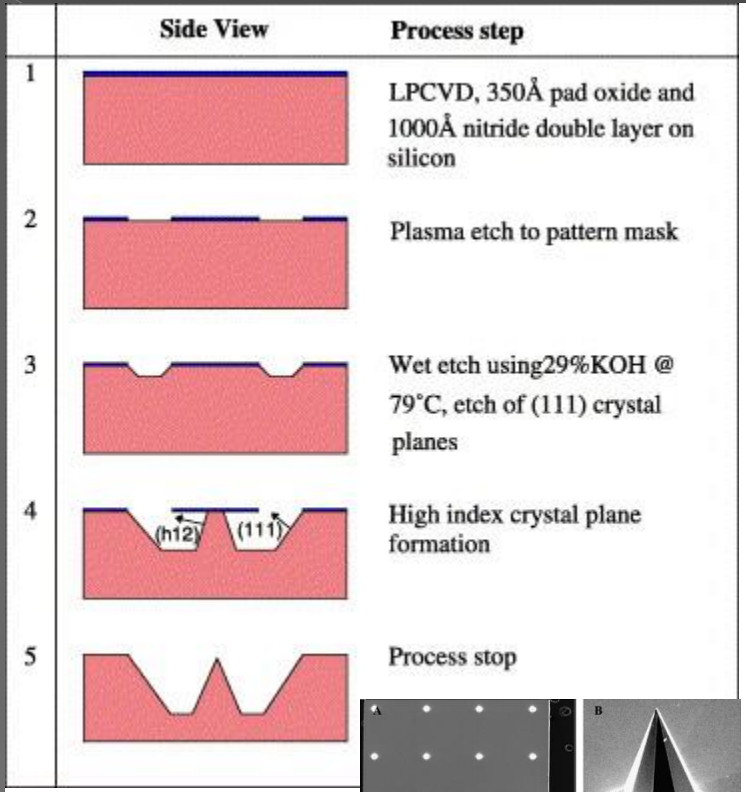
Lithography

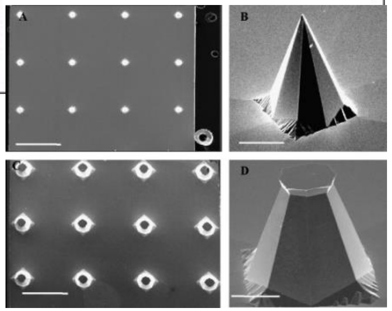


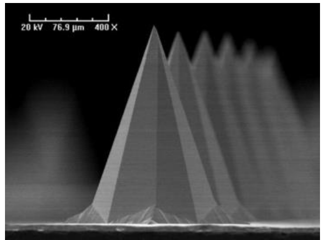


Lee & Jung (2012) *Biomaterials* **33** (30): 7309–7326

Wet Etching

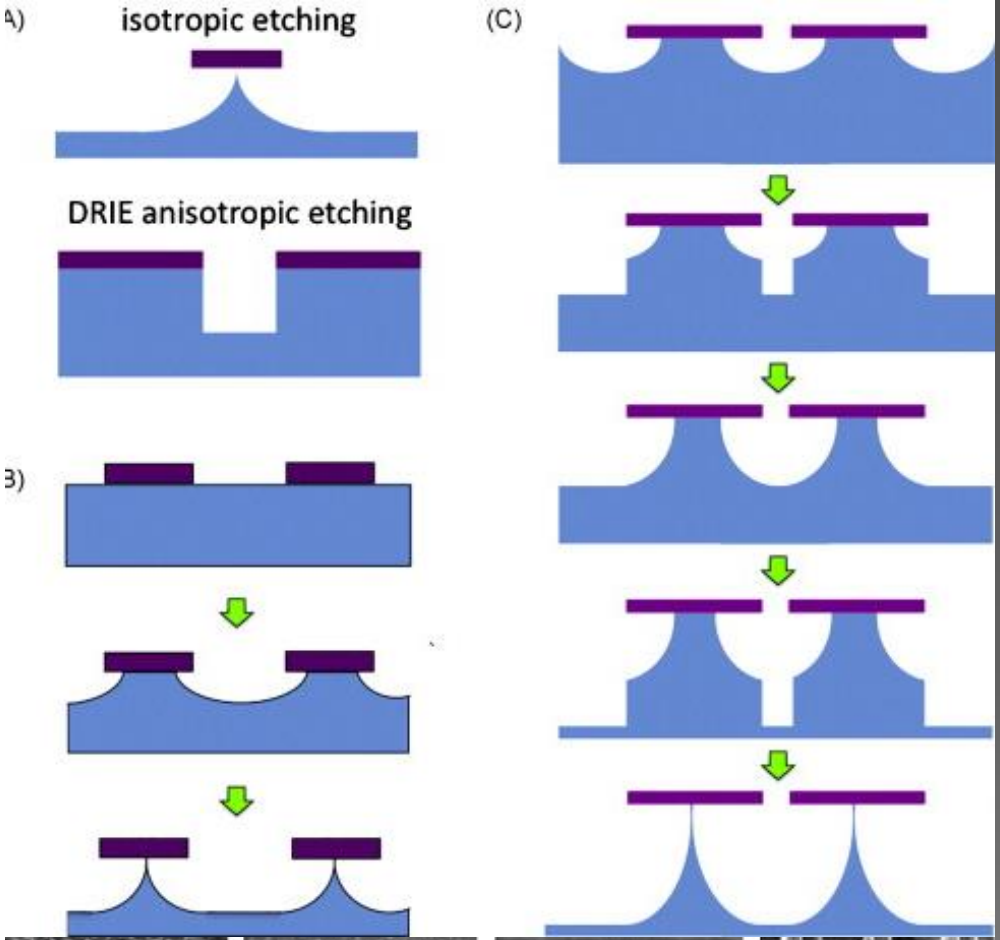


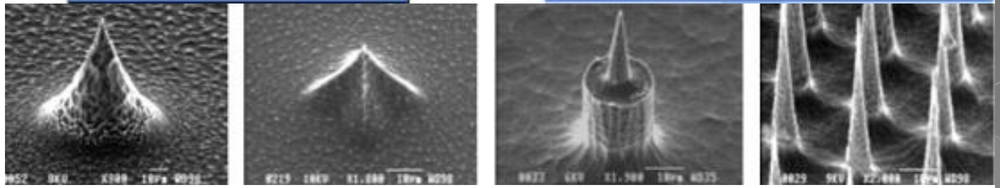




Morrissey *et al.* (2004) *Microelectronics Journal* **36** (7): 650–656

DRIE Etching

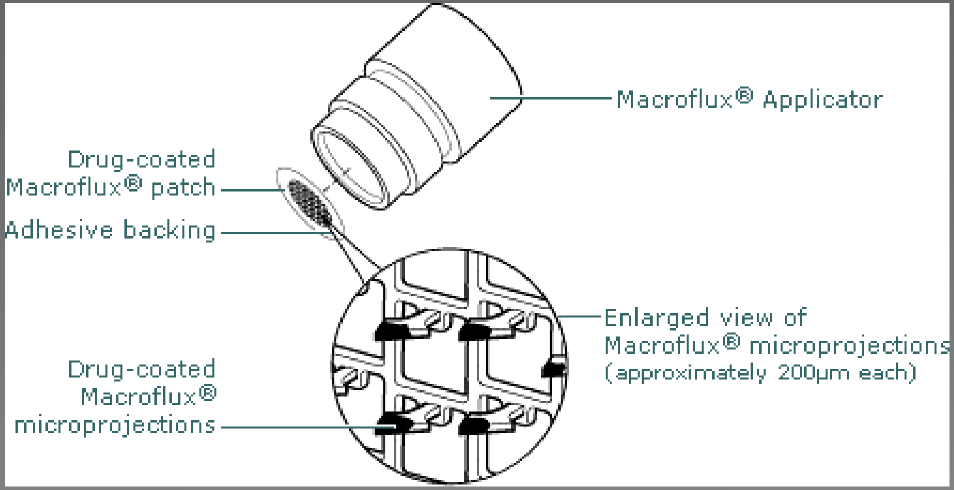




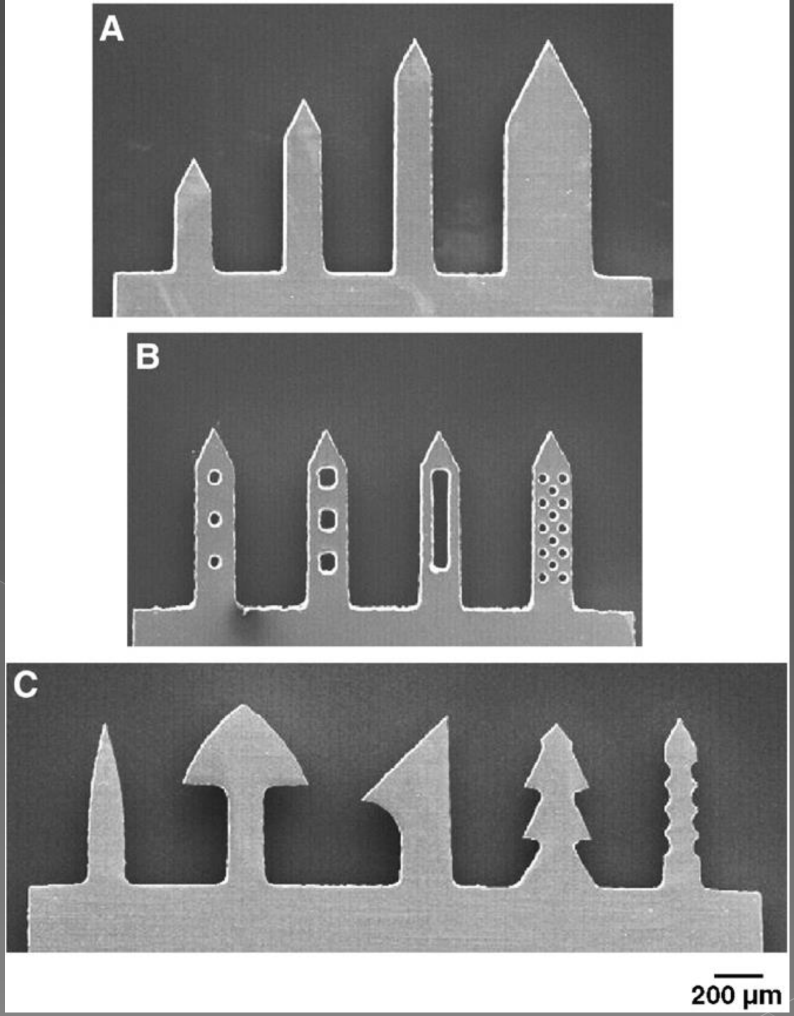
Charvet *et al.* (2010) Biosensors and Bioelectronics **25** (8):1889–1896

Metal Microneedles

- Typically titanium or stainless steel
- Laser cut to shape
- Can be used in-plane or bent out of plane

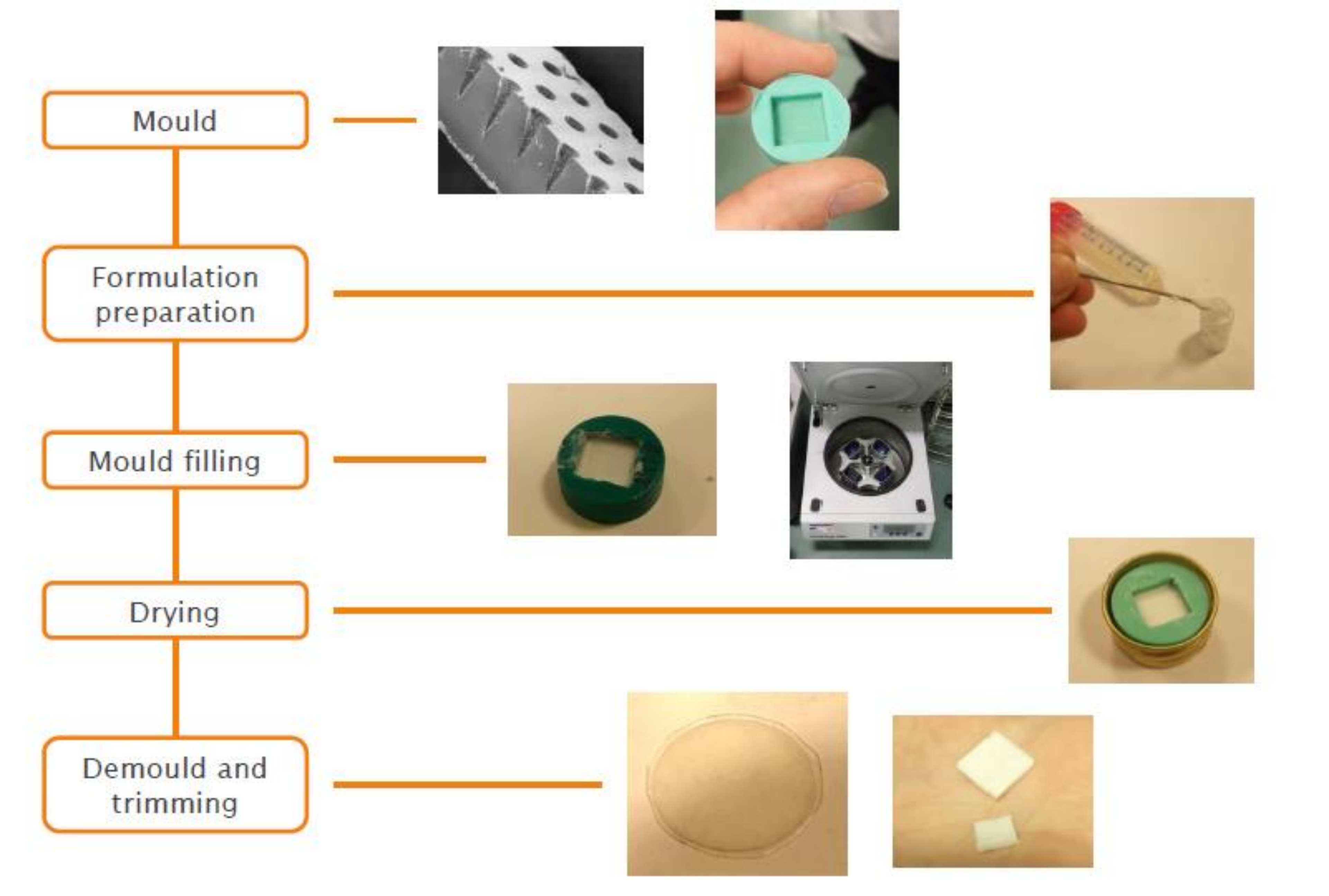


Macroflux® System (Zosano Pharma)

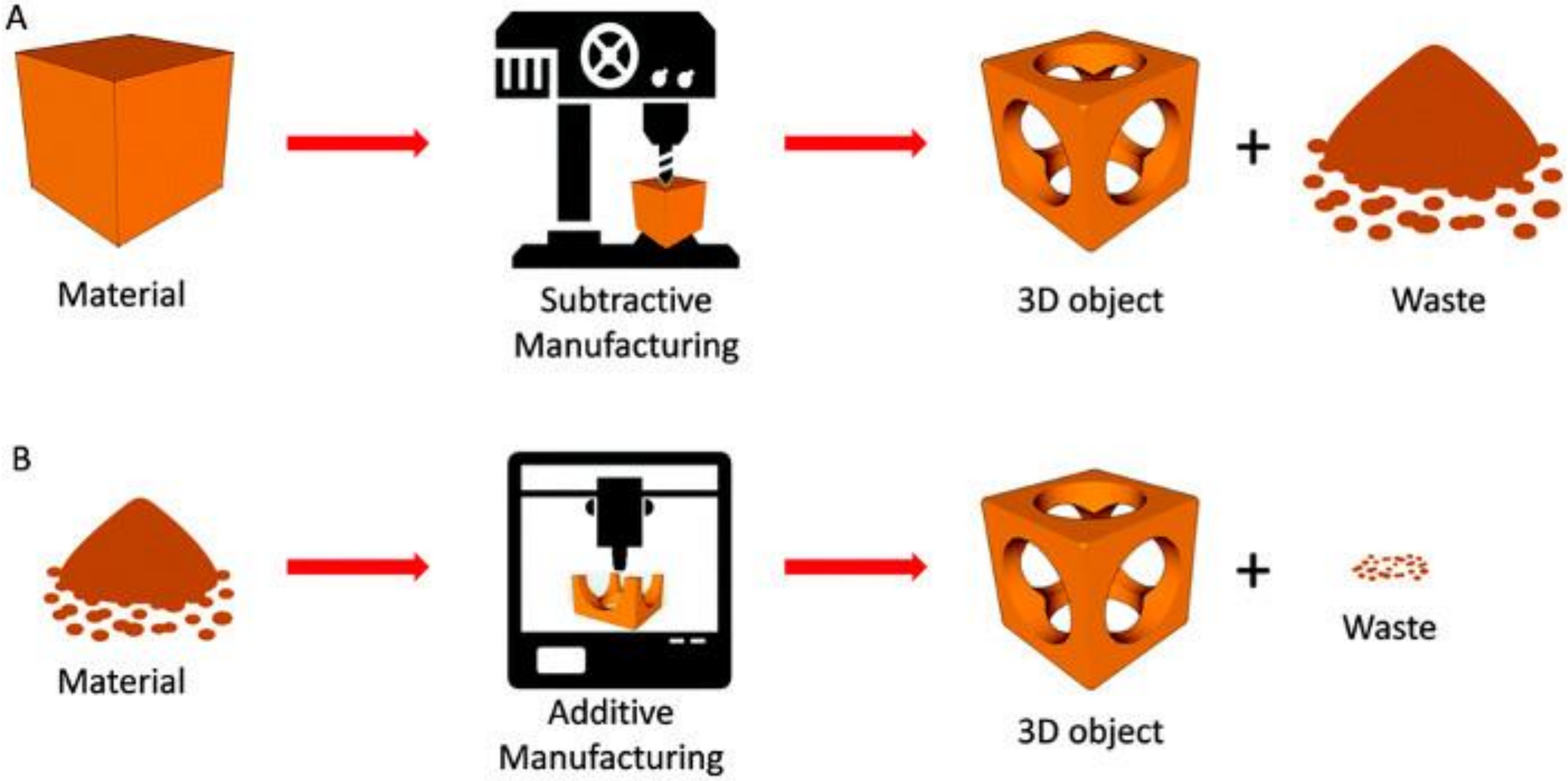


Gill & Prausnitz (2004) *J Cont Rel* **117:** 227-237

Micromoulding

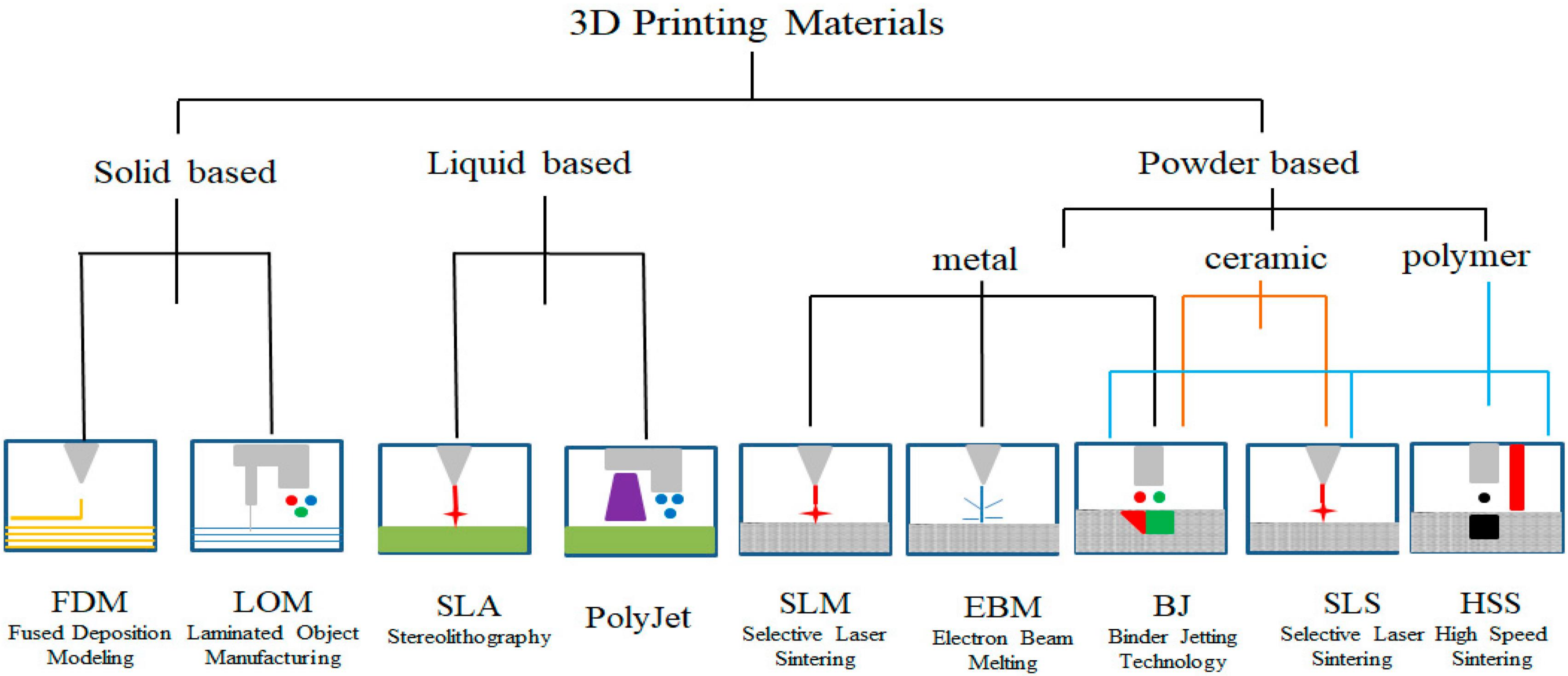


3D PRINTING


A
Material
Subtractive Manufacturing
3D object
+
Waste
B
Material
Additive Manufacturing
3D object
+
Waste

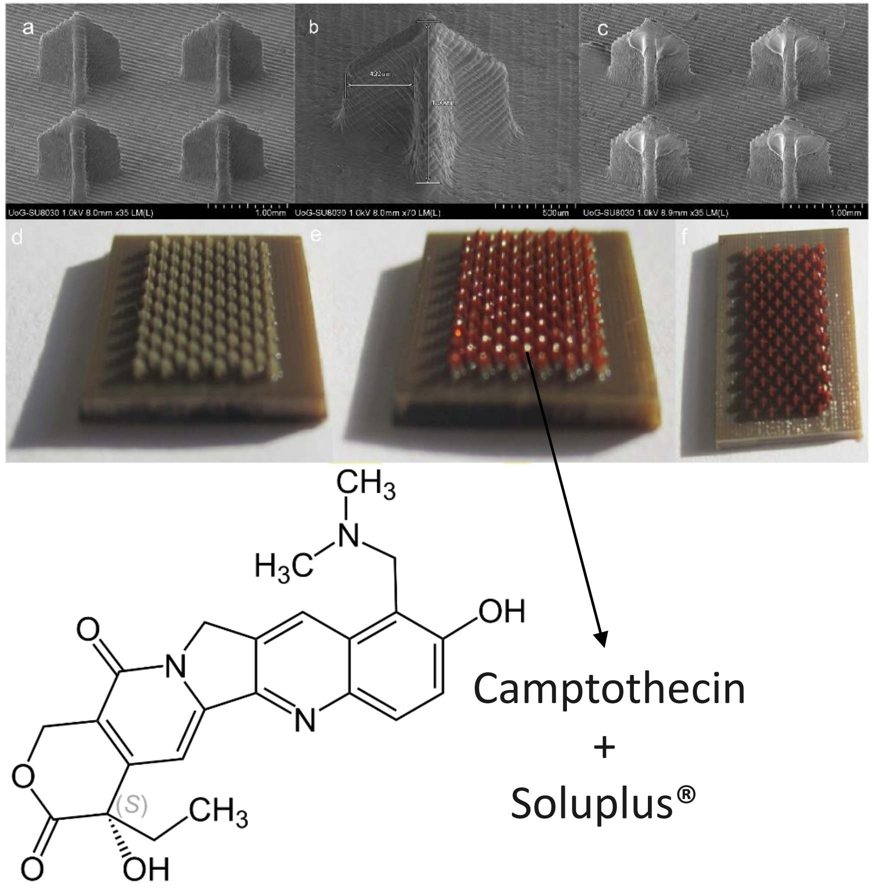
The main types of 3D printing types used for biomedical applications are:

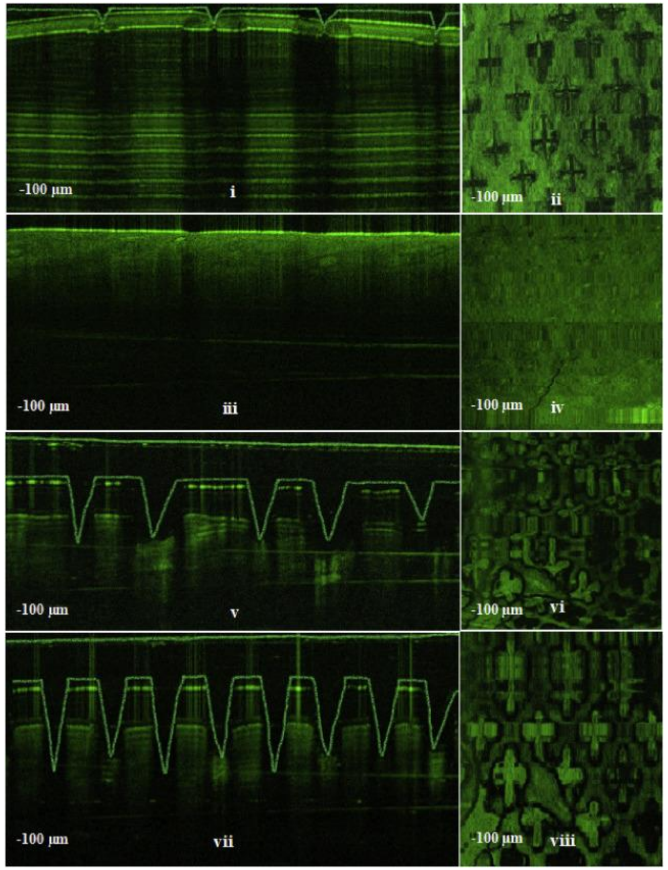
- Stereolithography (SLA)
- Fused deposition Modeling (FDM)
- Selective Laser Sintering (SLS)
- Inkjet Printing
- Bioprinting

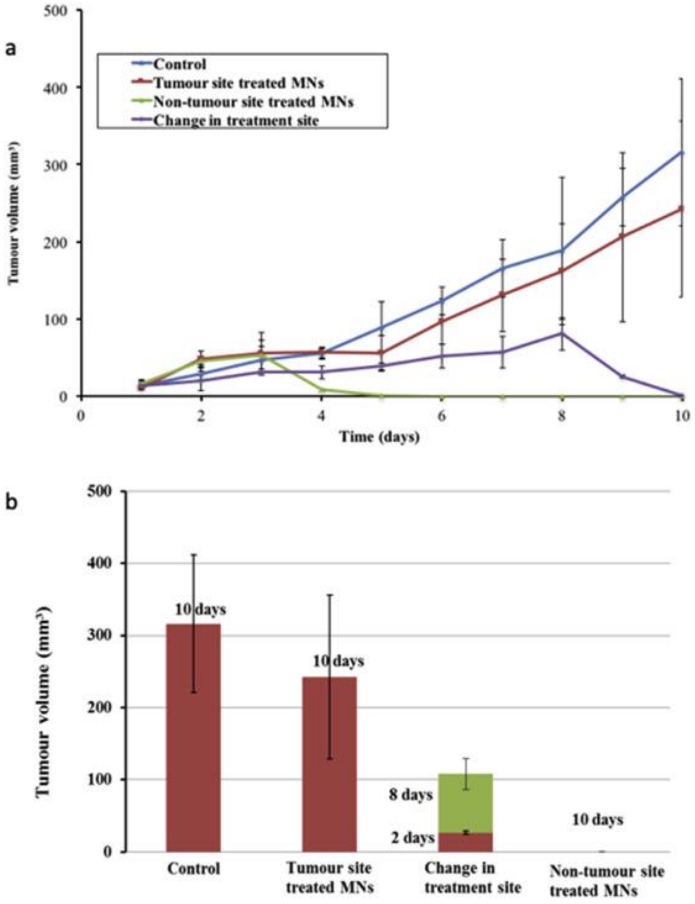


https://doi.org/10.3390/ma13102406

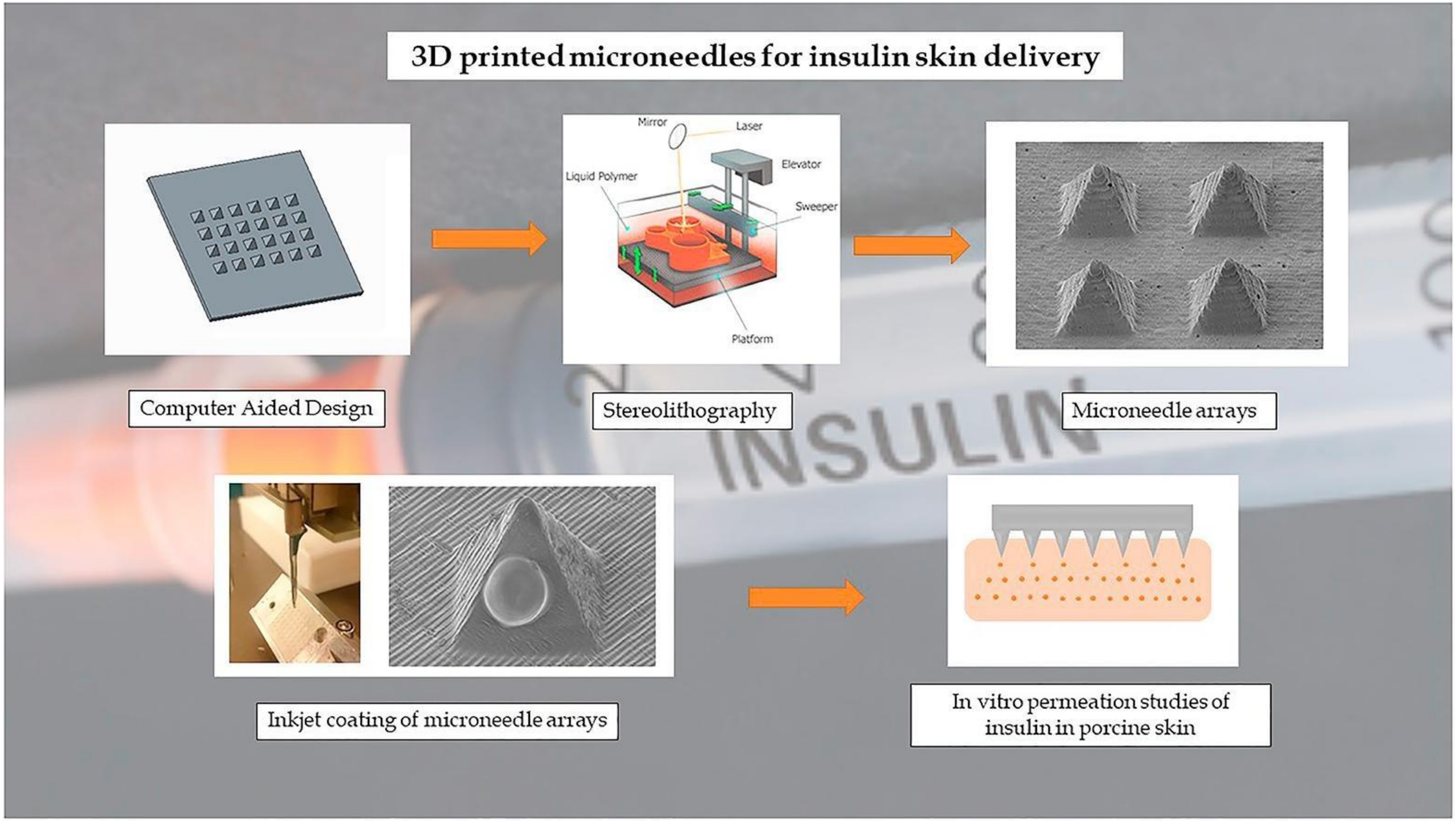
3D printed microneedles for anticancer therapy of skin tumours



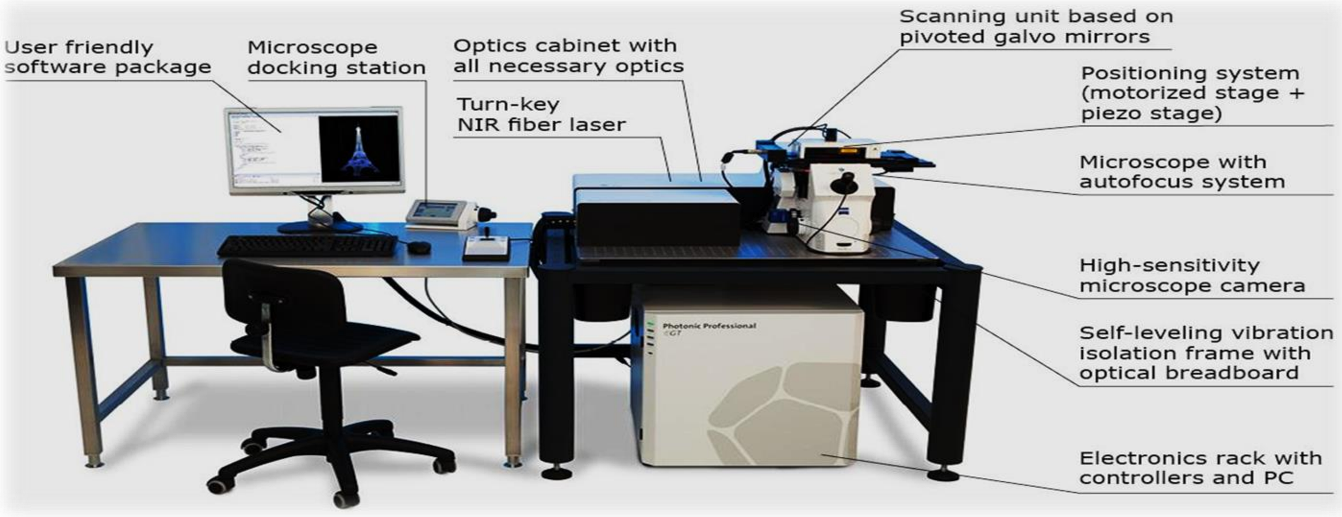


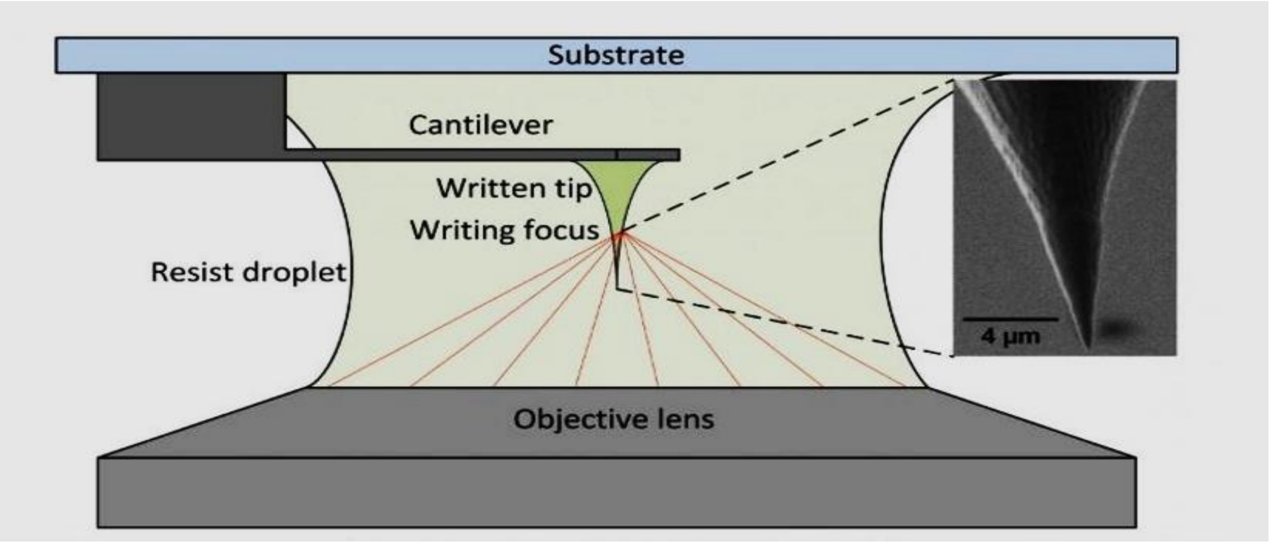


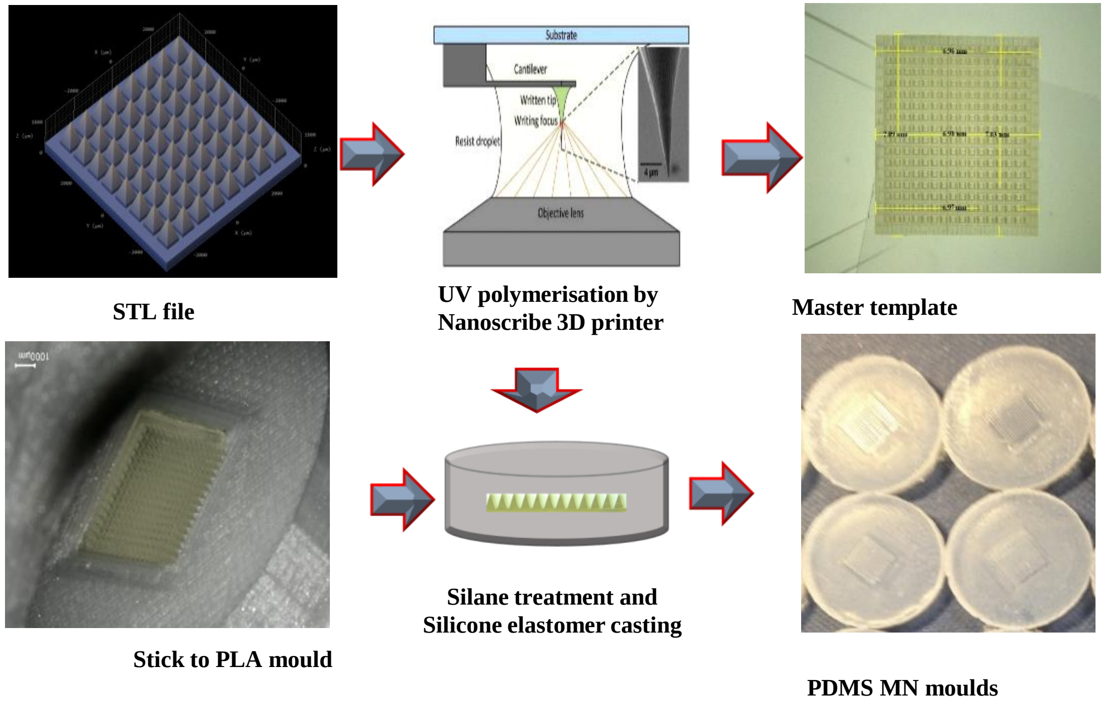
3D printed microneedles: Peptide delivery



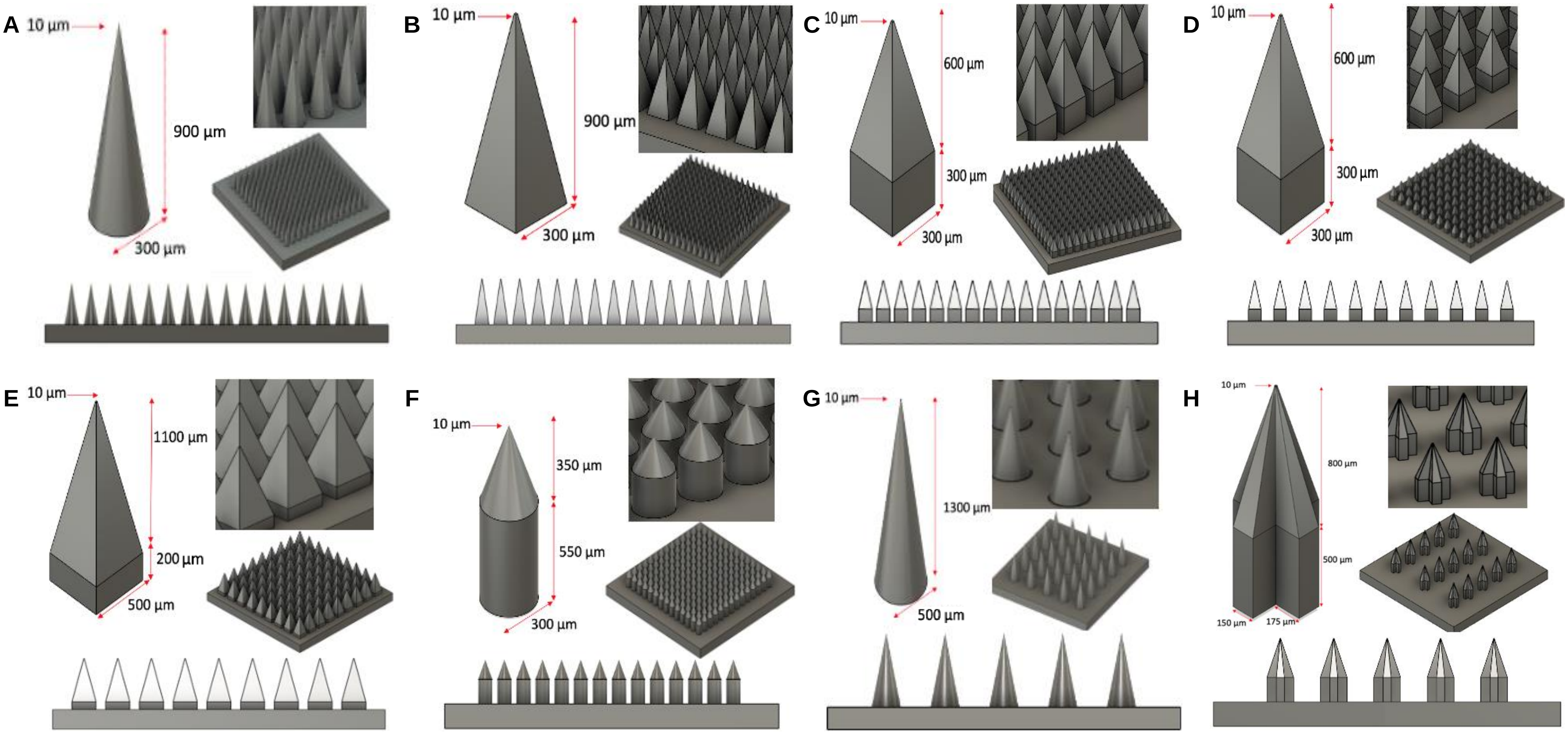
3D Printing of Microneedle Templates







Microneedle Designs



Process Rationalisation

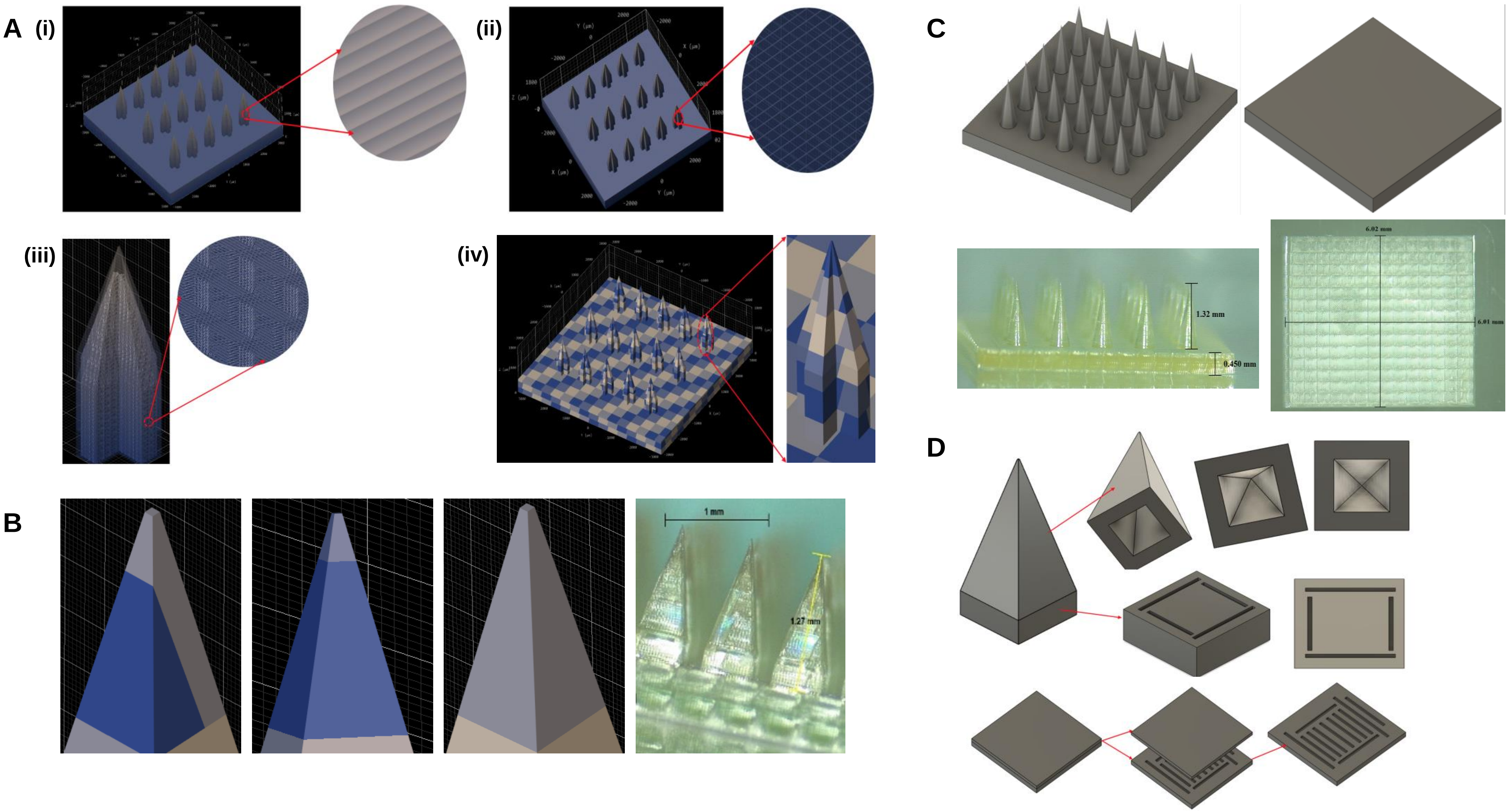
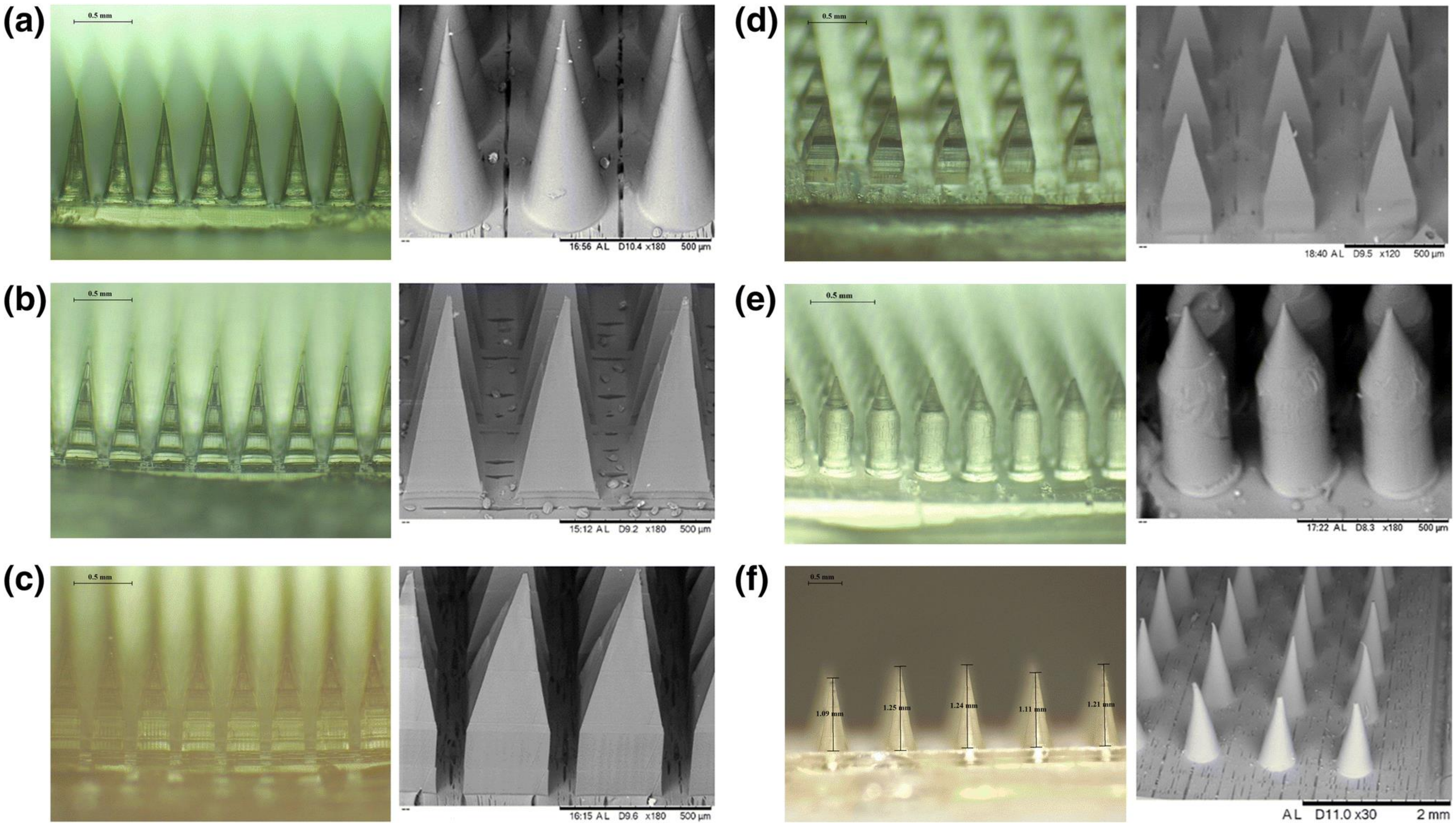


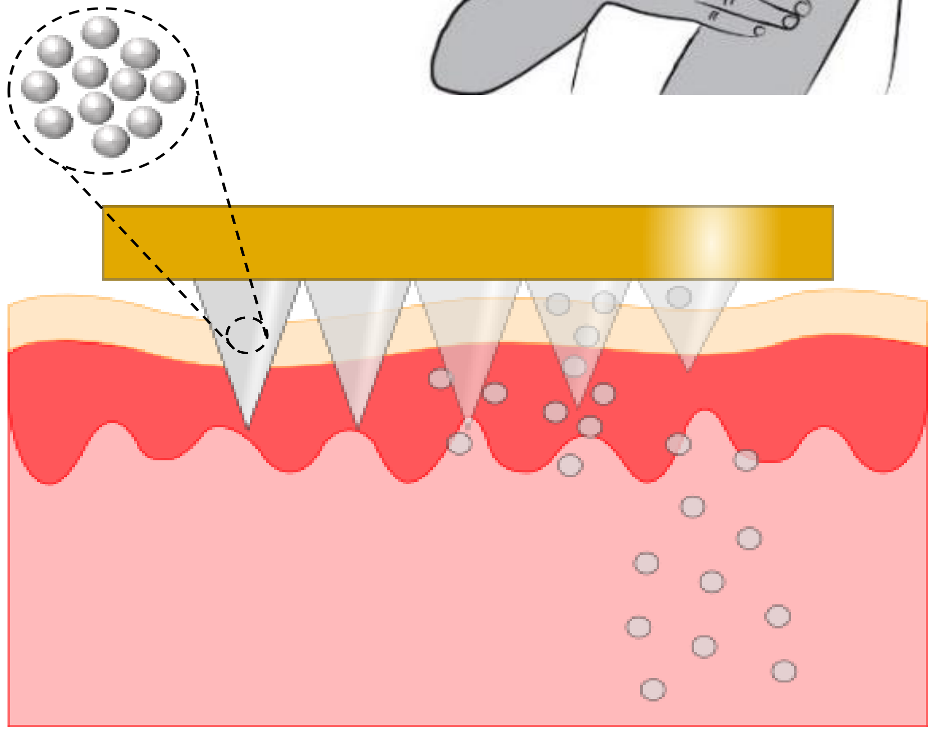
Figure 1. Optimisation of different 3D printing parameters: **(A) (i)** distance between different layers ("slicing"); **(ii)** shell parameters (distance between hatch lines, minimum shell contour count, and number of filled slices at the bottom of the shell); **(iii)** scaffold parameters (spacing between scaffold walls and floors, thickness of scaffold walls and scaffold floor); and **(iv)** splitting mode (block width in X and Y direction, block height and block offset in X, Y and Z direction); **(B)** effect of block size and position in printing the needle tip with (from left to right) two blocks, one short block in Z direction, and one single and large block (printed example); **(C)** Two-step 3D printing of long MN master templates (1.3 mm high needles) and additional baseplate; **(D)** cavities introduced in the MN, pedestal and baseplate designs.

Printed Microneedles

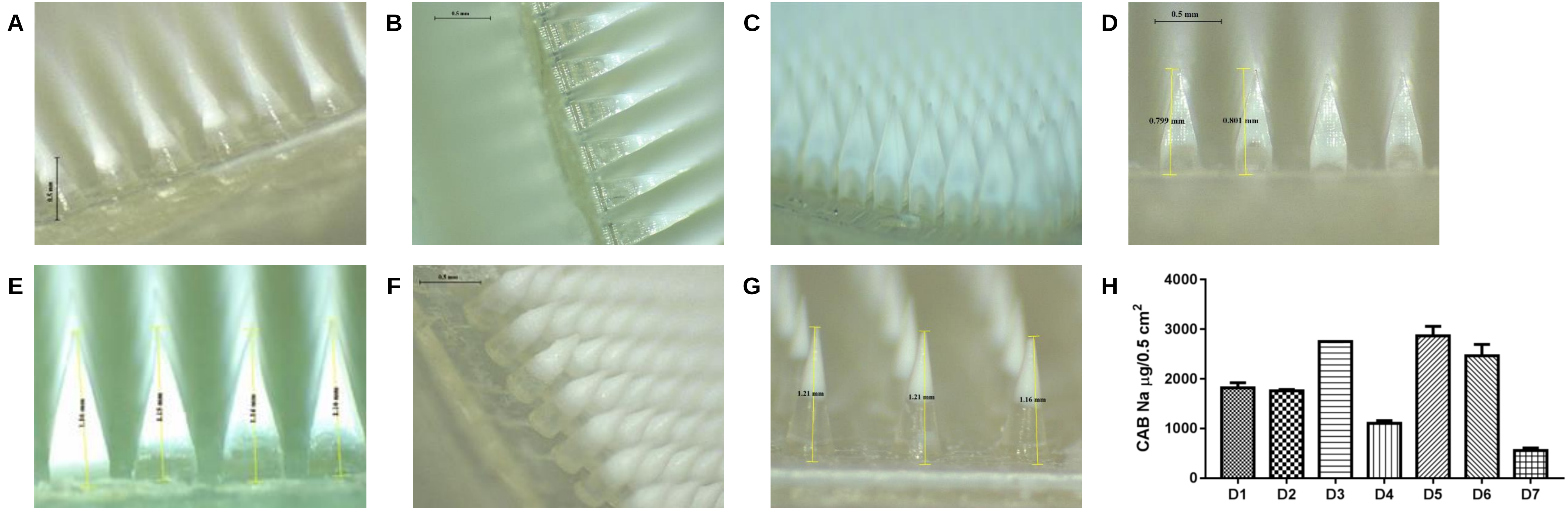


FORMULATION AND APPLICATION OF LONG-ACTING MICROARRAY PATCHES CONTAINING DRUG NANOSUSPENSIONS

- Load solid drug nanocrystals nanoparticles <u>at high concentration</u> into aqueous gels or make microneedle tips from biodegradable polymers
- Cast into mould <u>made from 3D-printed master template</u>
- Dry and add border adhesive and occlusive backing layer to form microarray patch (MAP)
- Baseplate should readily detach upon microneedle dissolution in skin
- Nanoformulated/controlled release drugs deposited in viable skin layers for sustained release and absorption by rich dermal microcirculation

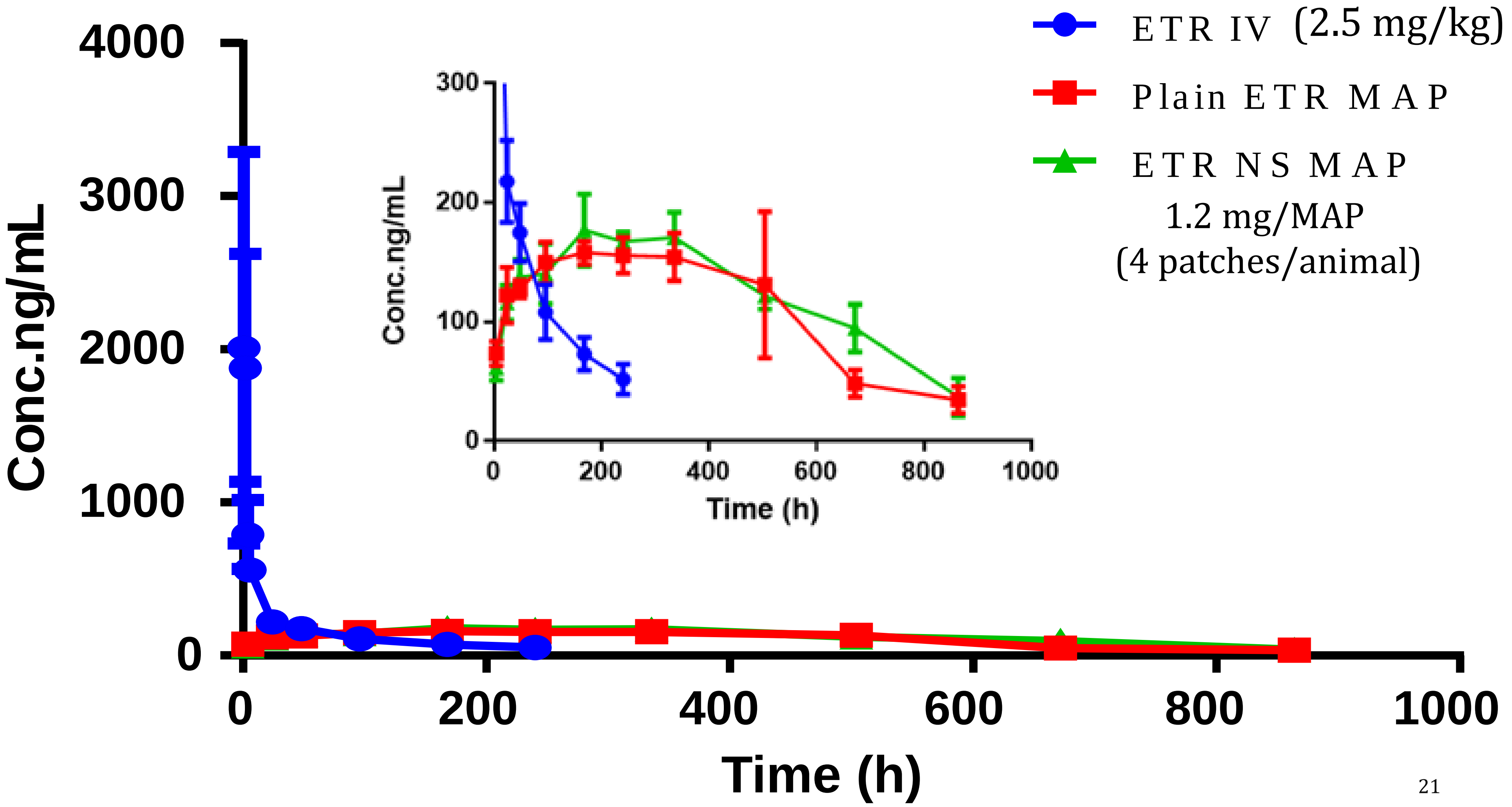


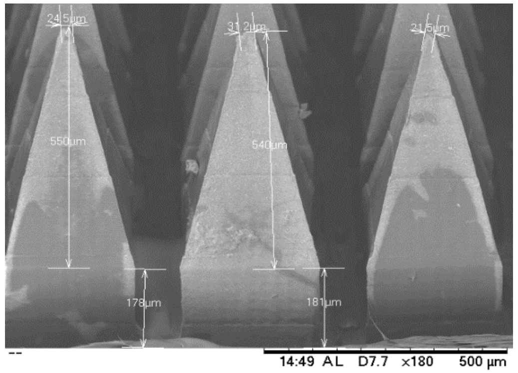
Micromoulded Microneedles

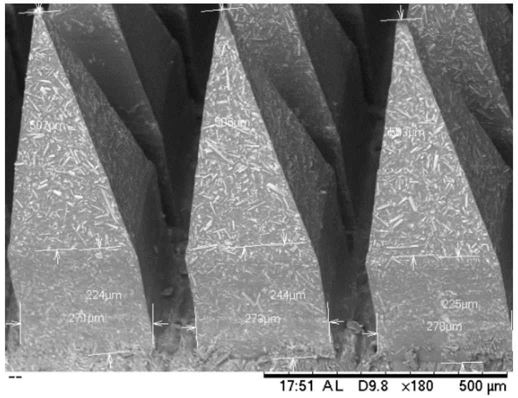


Etravirine-loaded dissolving microneedles

In vivo study- PK profiles







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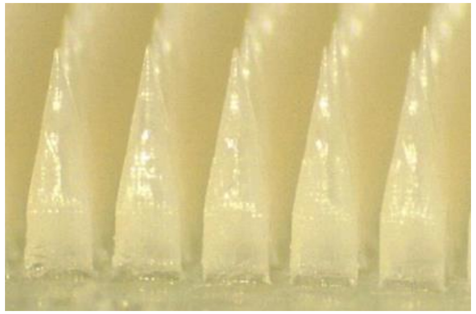
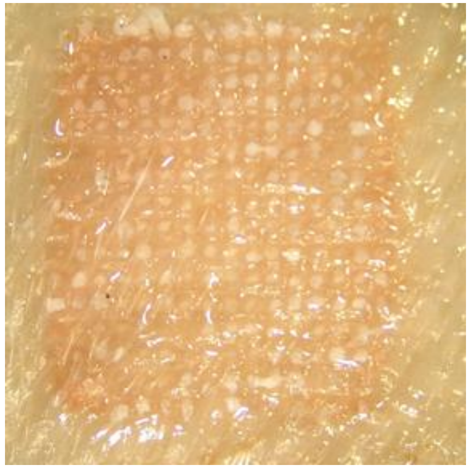
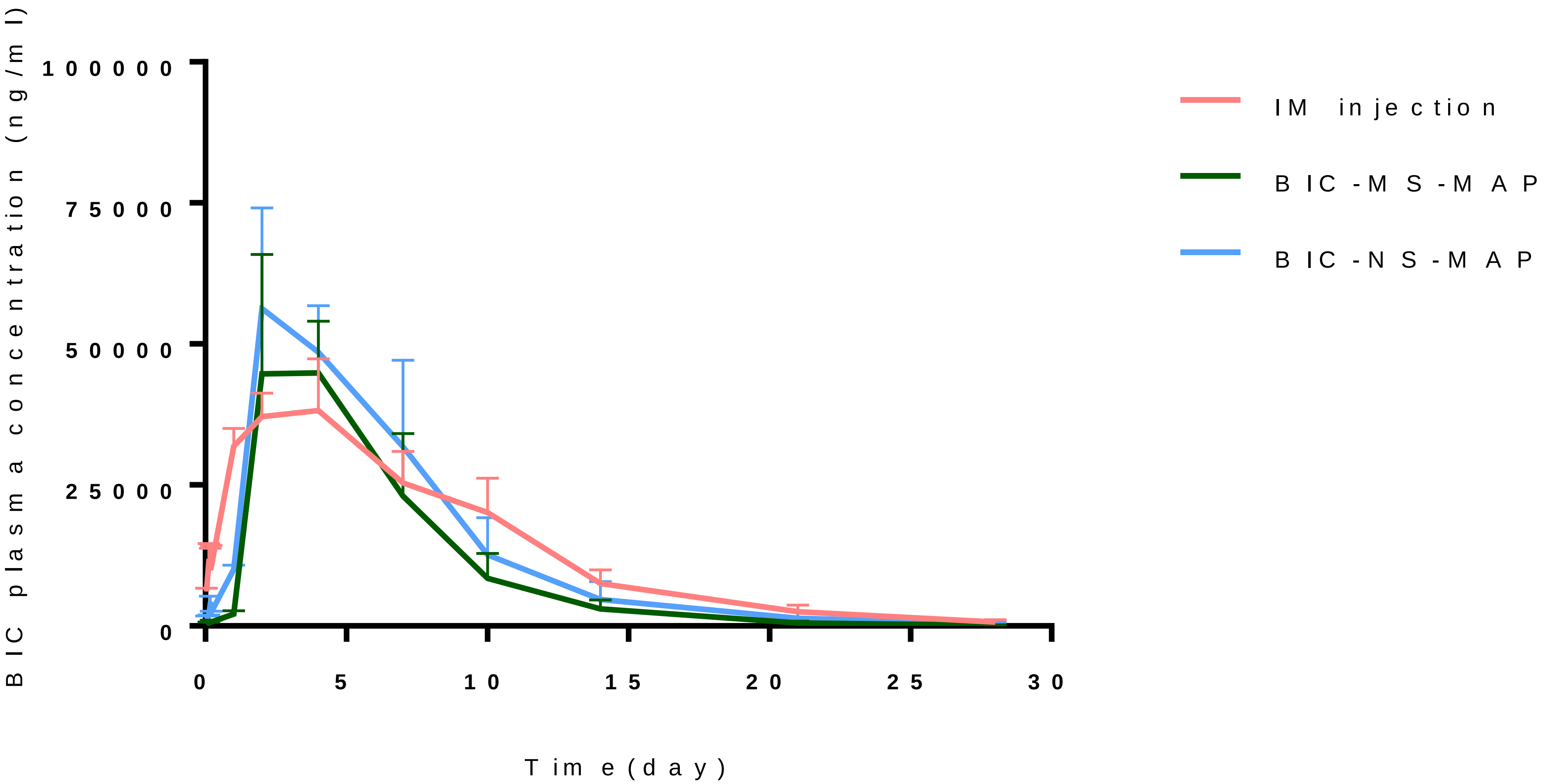
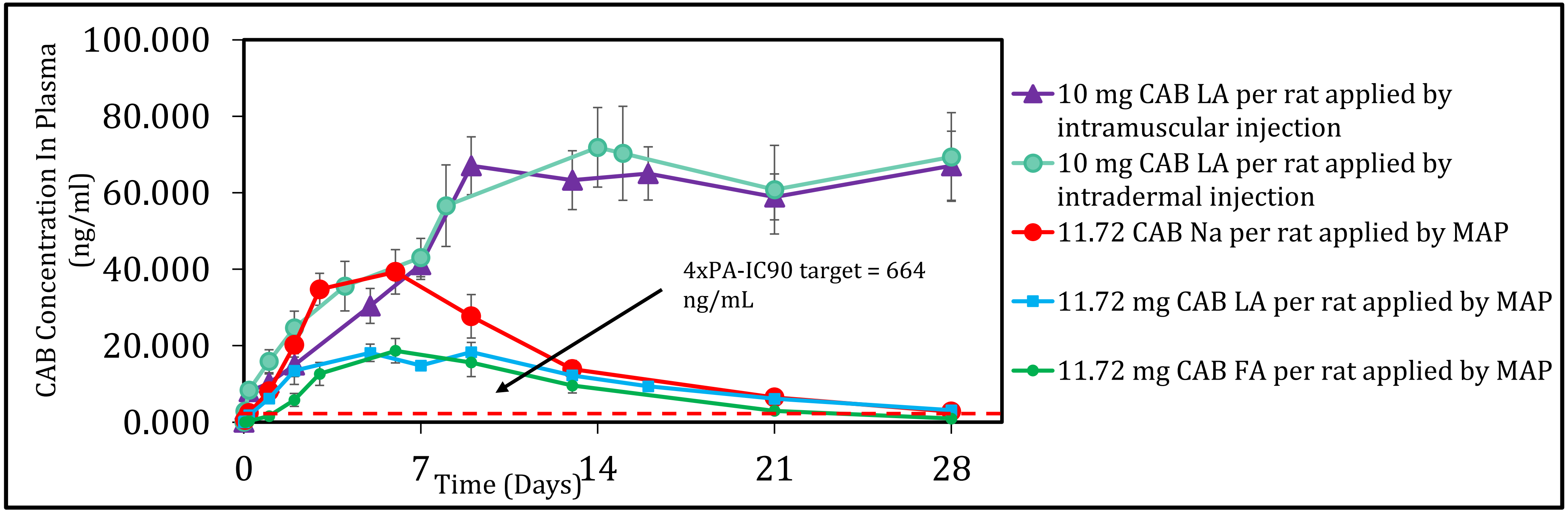
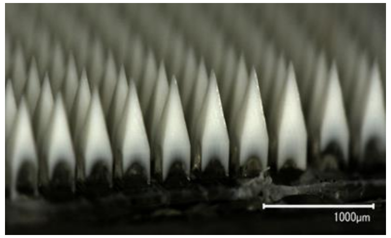


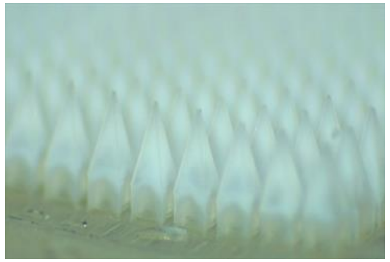




CABOTEGRAVIR *IN VIVO* STUDY

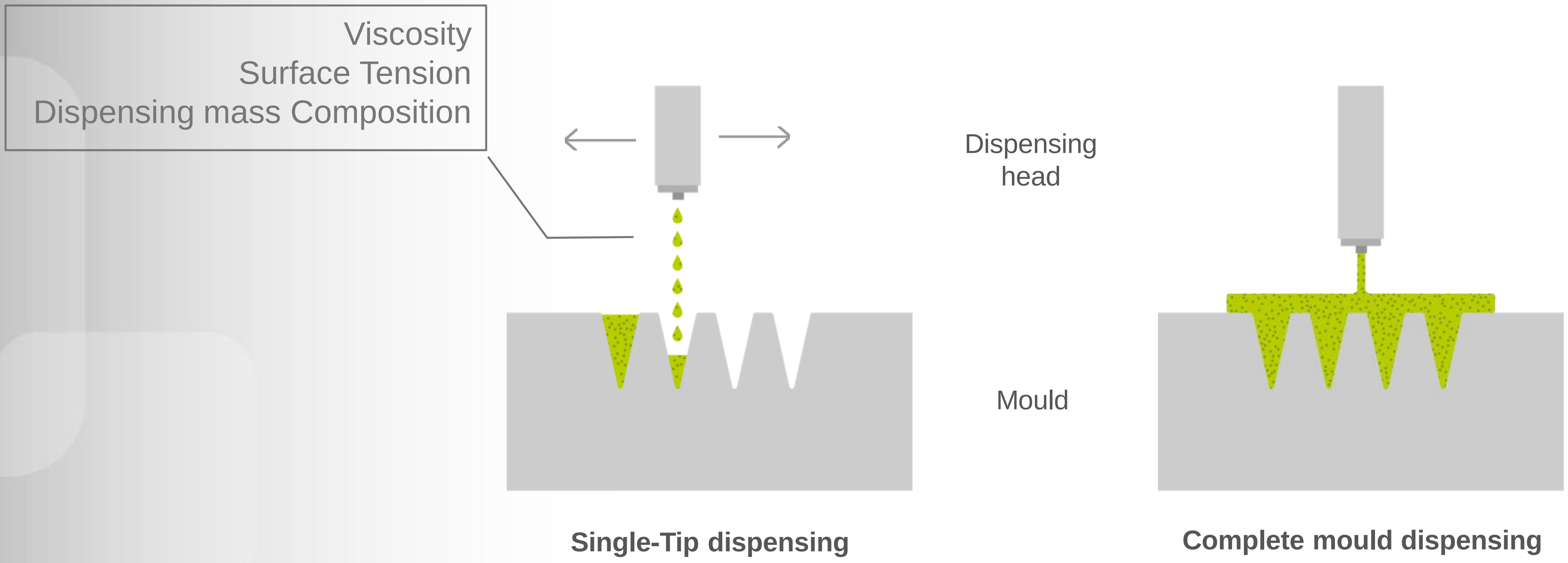




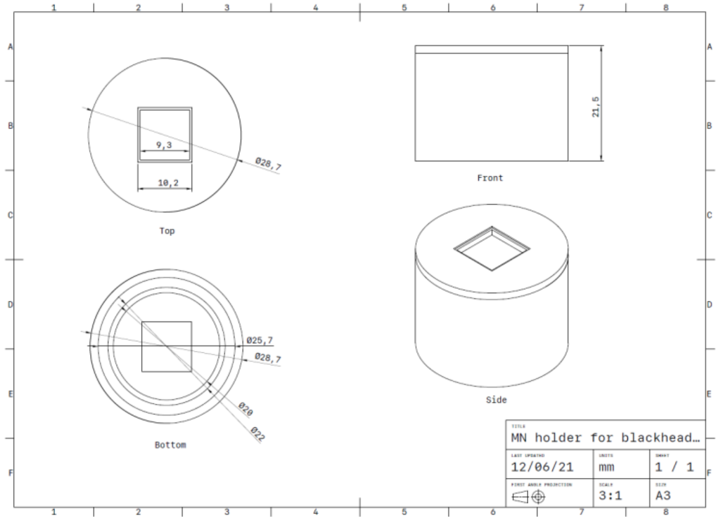


INDUSTRIAL MANUFACTURE OF TIP-LOADED POLYMERIC MICROARRAY PATCH SYSTEMS

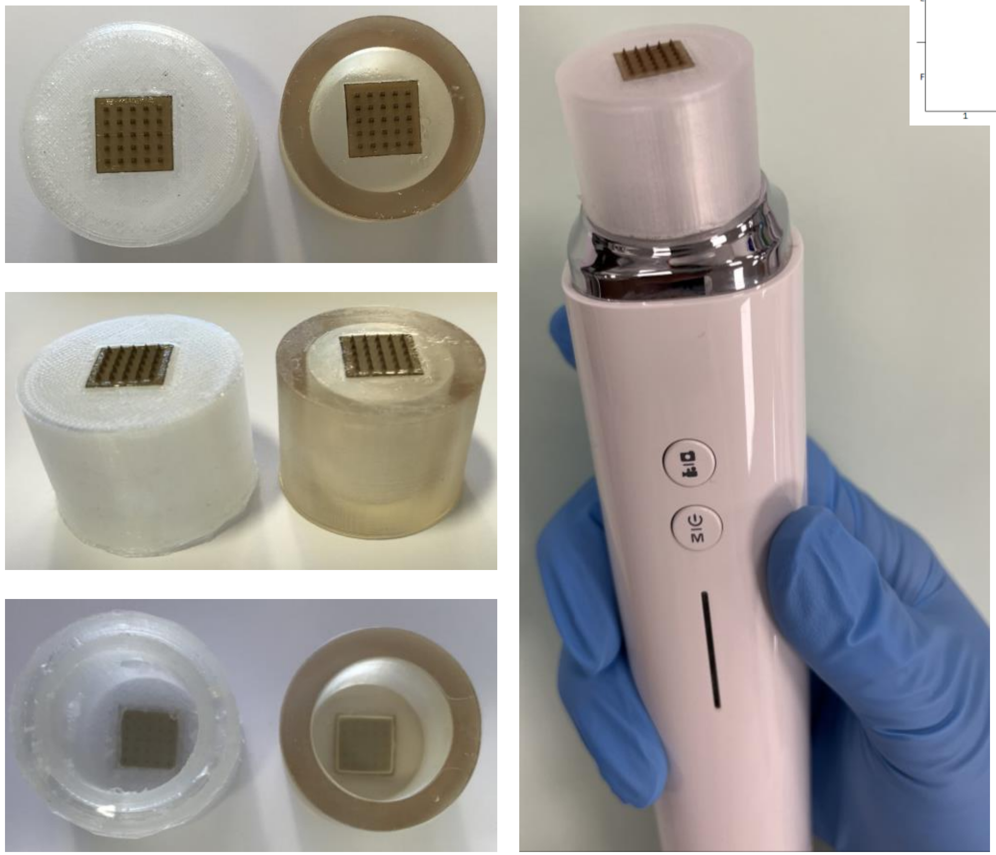
Dispensing



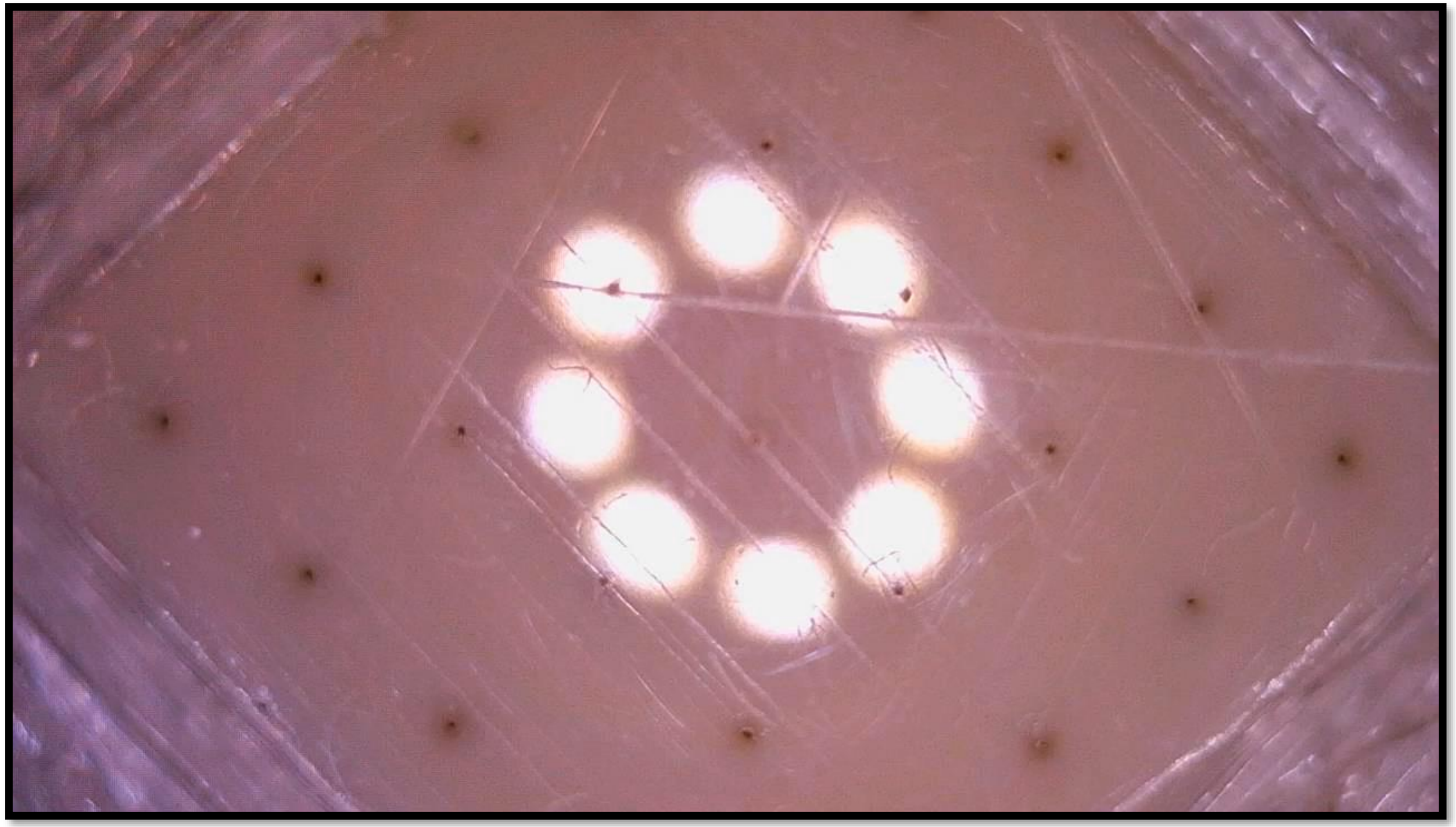
Hollow microneedles and suction device: Application to interstitial fluid extraction



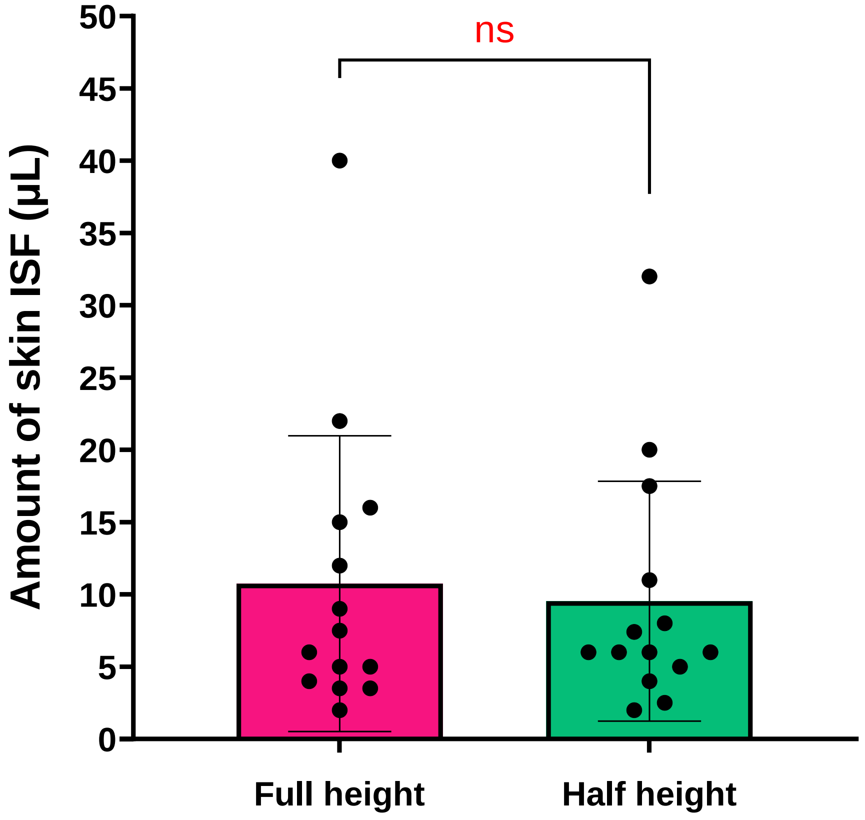
- The MN holders were prepared using FDM- and SLA-3D printers.
- Polypropylene (PP) filament and clear basic resin were used as a printing material for FDM and SLA printers, respectively.
- The MN holders printed by the FDM 3D printer offered greater consistency in terms of fitting to the suction device when compared to the holders printed by the SLA 3D printer. This is a result of a void area between the walls of the holder and the elasticity of the printing material.



Hollow microneedles and suction device



Hollow microneedles and suction device



- The liquid uptake study was conducted using MN holders with different heights.

- The hollow MNs were inserted into porcine skin and the suction device was operated at the maximum power level for 3 minutes.

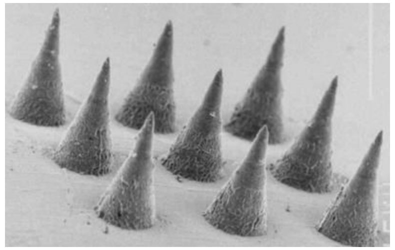
- The skin ISF was collected from the MN holder and the suction device (if any) using glass capillary tubes.

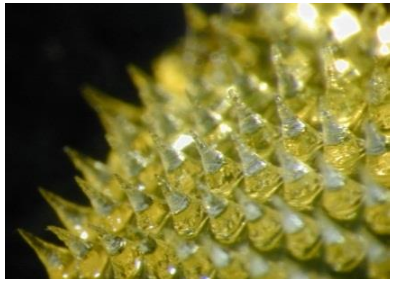
- It was observed that decreasing the height of MN holders did not significantly affect the amount of skin ISF extracted by the suction device (two-tailed *t*-test, p-value > 0.05).

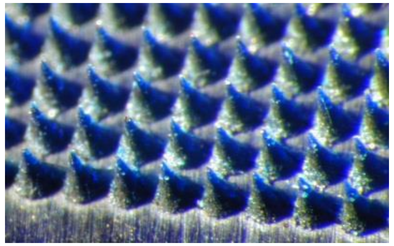
- The MN holder with a height of 21.5 mm can extract the skin ISF in the range between 2–40 µL (n = 14).

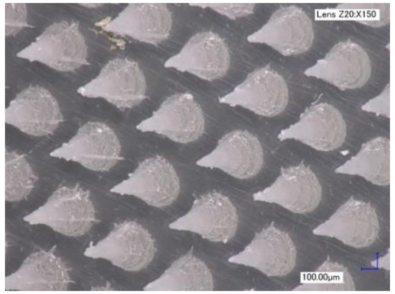
- The MN holder with a height of 11.5 mm can extract the skin ISF in the range between 2–32 µL (n = 14).

NEXT STEPS IN DEVELOPMENT









- Microneedle systems have <u>great</u> potential for delivery of a range of drugs and can be useful in blood-free patient monitoring/diagnosis.
- 3D printing can be useful in manufacture
- Potential to address a range of global healthcare challenges
- Great strides being made on manufacture and regulatory development – Significant investment from Big Pharma
- Major EPSRC programme: De-risk delivery platforms in accordance with regulatory advice: Develop a bridging programme applicable to any drug to be delivered
- Further development needed on microneedle extraction/sensing systems, but regulatory path is shorter
- Commercialisation and patient benefit

Queen's University Belfast – School of Pharmacy

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