University of Kent

the UNIVERSITY of GREENWICH

3D PRINTED MICRONEEDLES COMBINED WITH A MICROELECTROMECHANICAL SYSTEM (MEMS) FOR TRANSDERMAL DRUG DELIVERY

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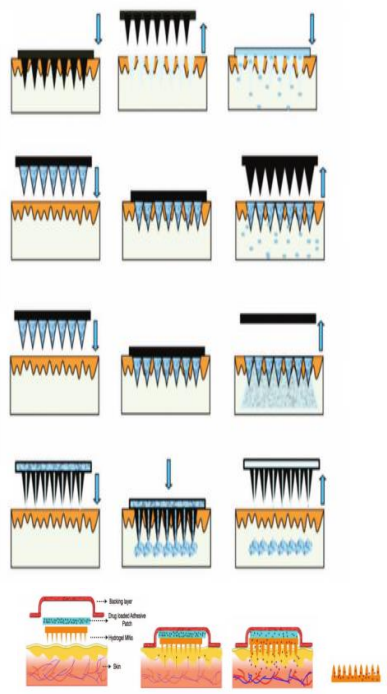
3D Printing

3D printing for microneedles (MNs)

- ✓ Allows easy and fast personalization and customisation according to application.
- ✓ Permits tailoring of dosages.
- ✓ Circumvents pitfalls associated with micromoulding and micromachining such as multiple steps and difficulty to customize.



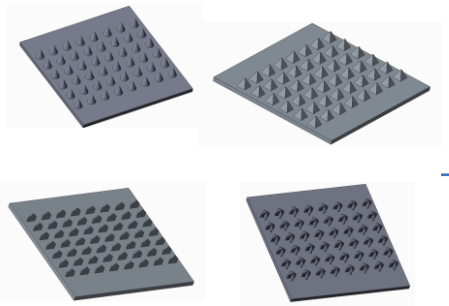
Stereolithography (SLA) is a 3D printing technique that enables the fabrication of structures through the consecutive layer-wise polymerization of light-sensitive polymers, through a curing process named photopolymerization.

Printing process

✓ Form 2 by Formlabs ✓ Class I biocompatible resin

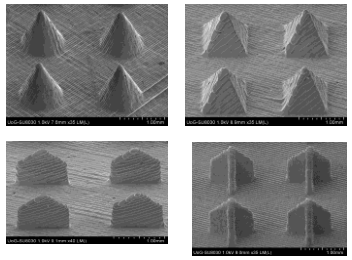
Alkilani et al. (2015) Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics, 7(4), 438–470.

Previous work: 3D printed solid MNs

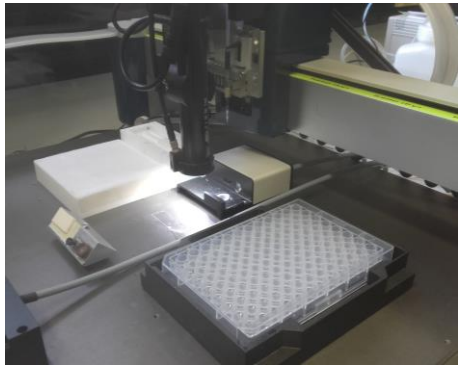


Design

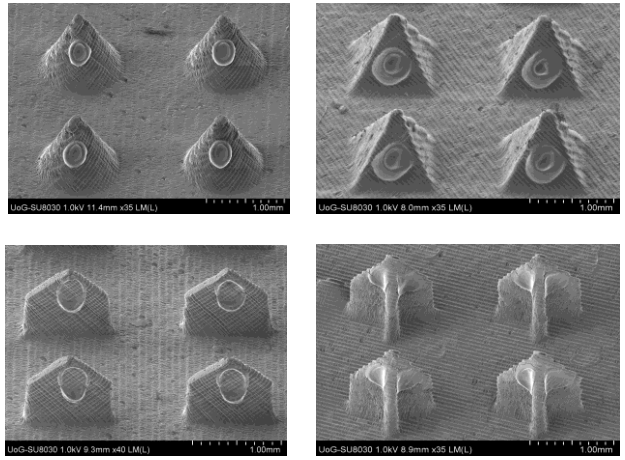
3D printing



3D printed MNs

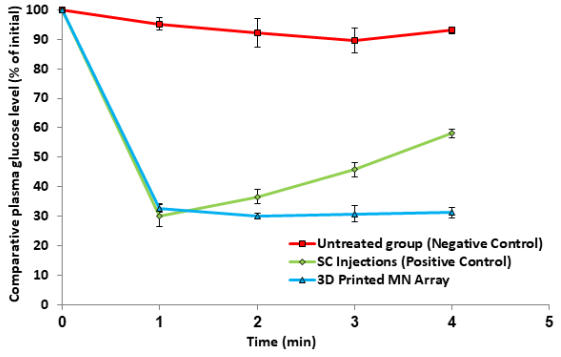


Coating with nanoplotter

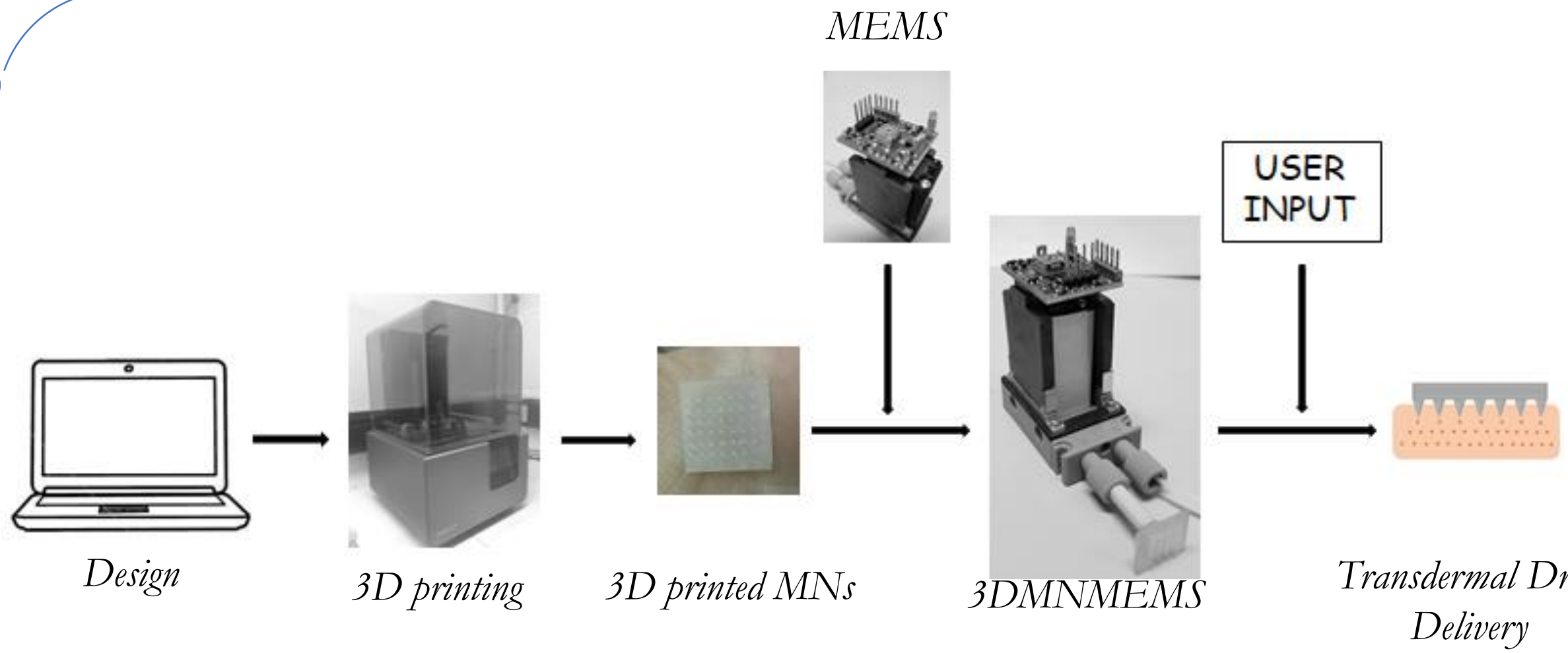


Coated 3D printed MNs

In vivo studies

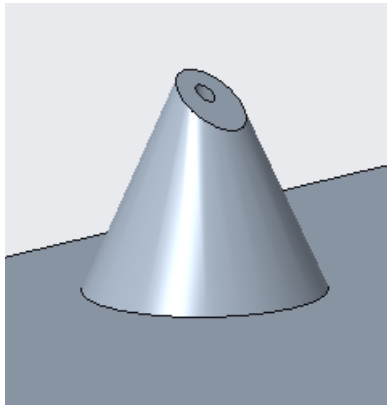


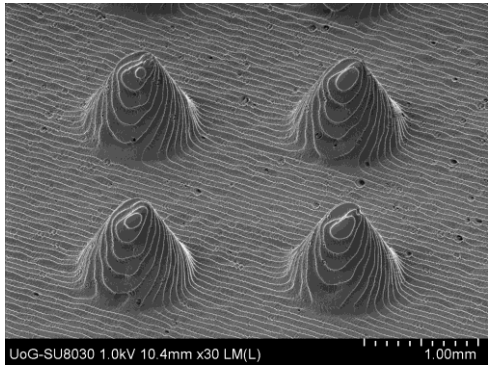
3D printed MN MEM system



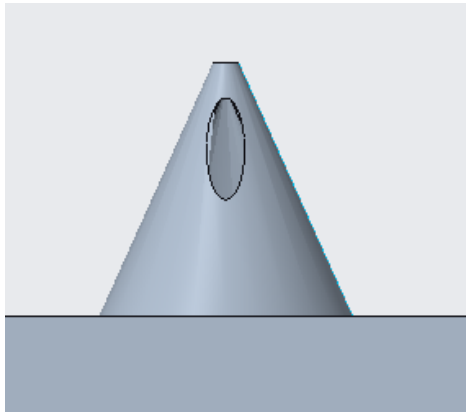
Microneedle Design and SEM

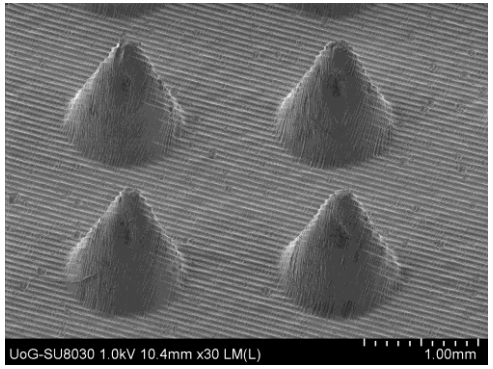
Bevel-type



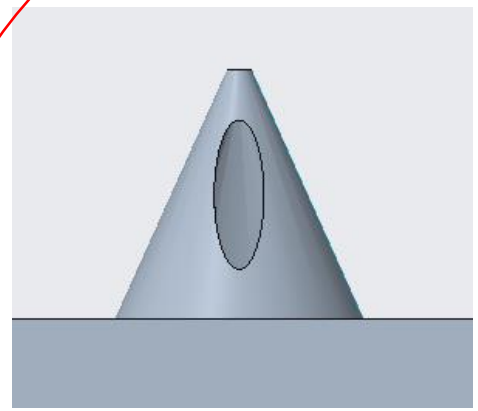


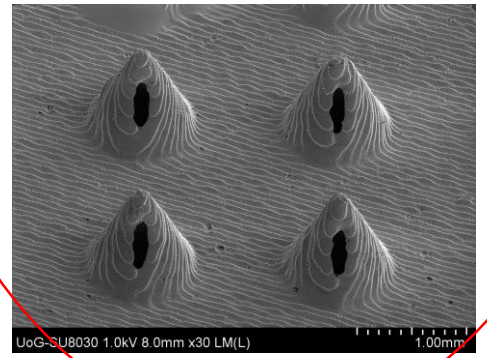
Ellipsis 1





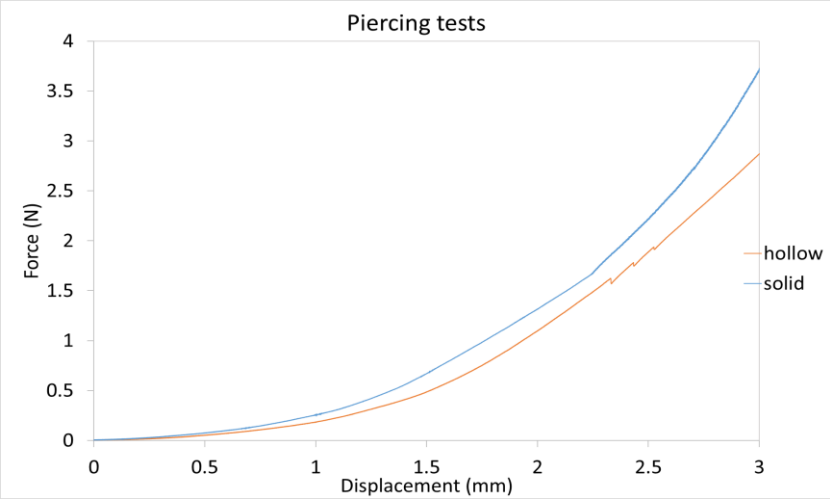
Ellipsis 2

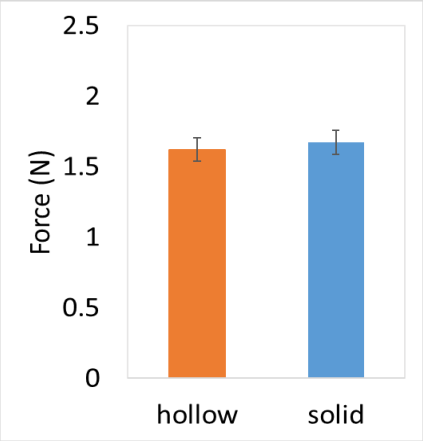




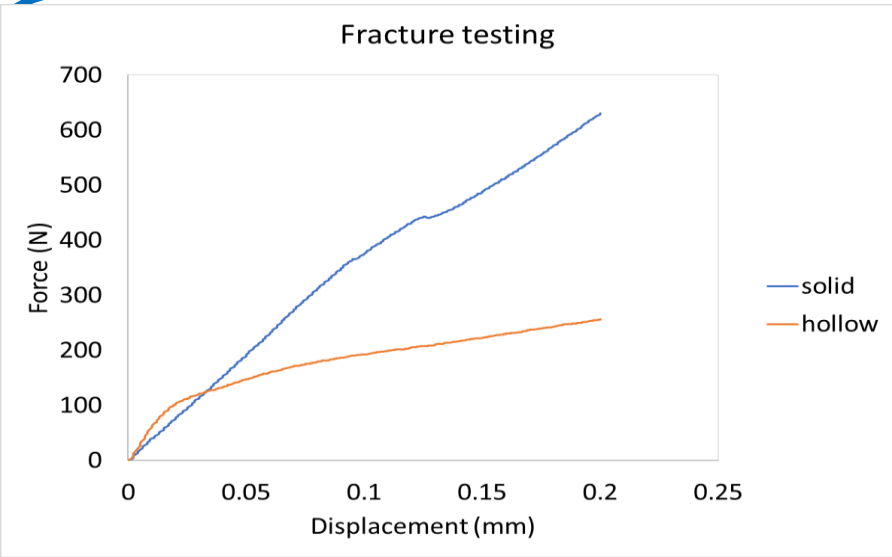
Resolution restrictions posed by the 3D printer

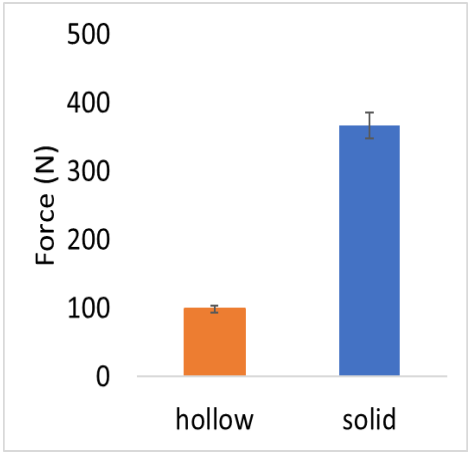
Fracture and piercing tests





- ✓ No MN failure
- ✓ Linear region: Elastic response of the skin
- ✓ Divergence from linearity: Small penetrations where the MNs gradually tear the skin
- ✓ Discontinuity: A threshold force is reached.





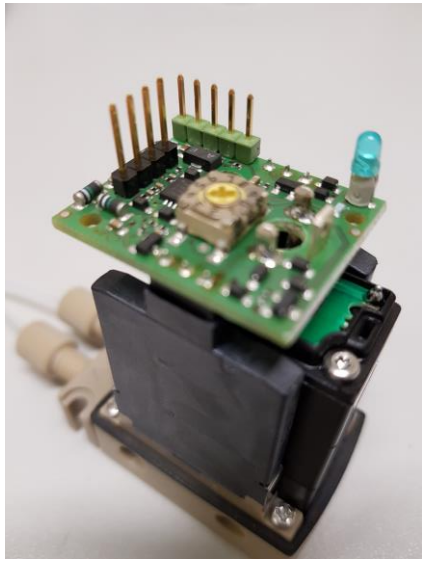
- ✓ Hollow and solid 3D printed MNs exhibited different modes of failure.

Margin of safety
Hollow : 60
Solid : 220

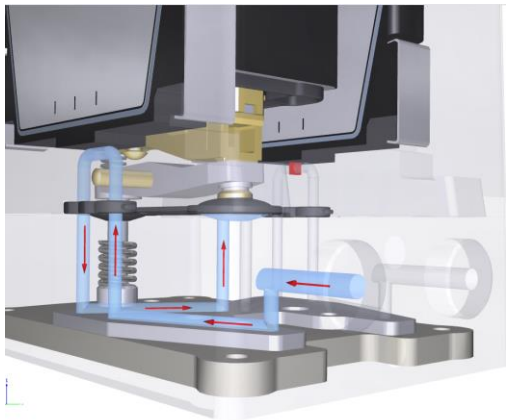
Microelectromechanical system

Customised diaphragmatic microdosing pump

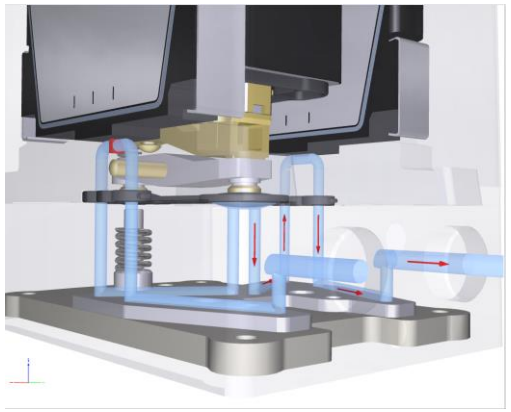
- ✓ Pumping of very small volumes, down to 5 µL
- ✓ Permits the regulation of the amount administered as well as the frequency
- ✓ Allows reversible flow
- ✓ Easy to handle and set by the user
- ✓ Works on electrical source or can be portable using batteries (24 V)



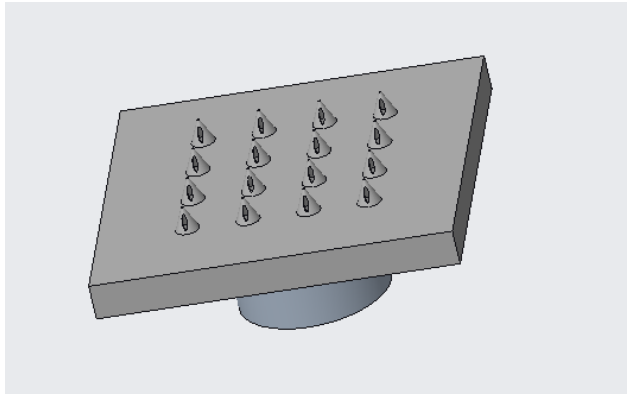
Pumping process

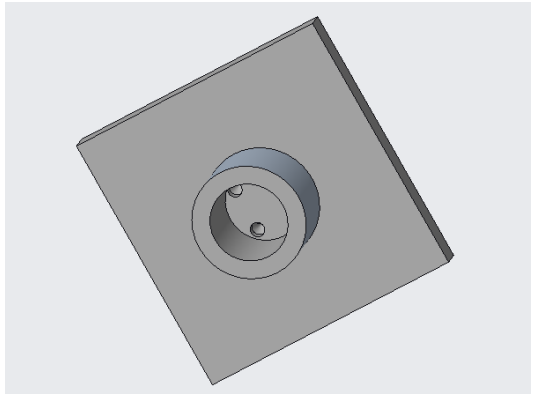


1. The diaphragm opens and the piston draws the fluid in

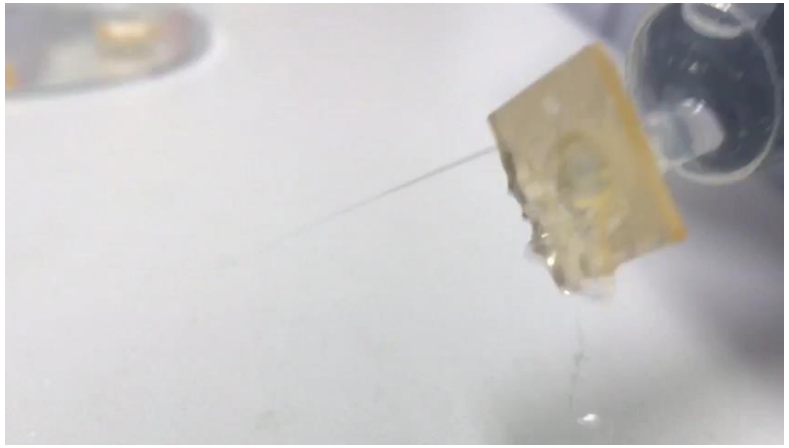


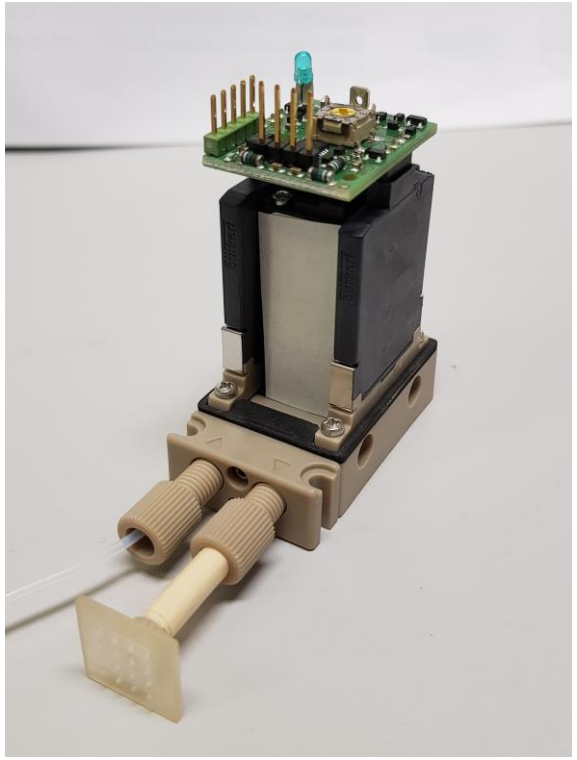
2. The diaphragm closes and the piston pumps the fluid out





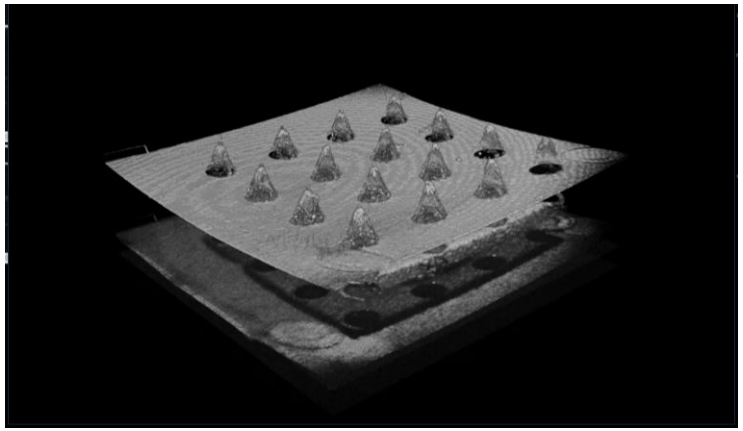
Patch featuring hollow MNs
The fluid is supplied from the main orifice to the MNs through an internal reservoir

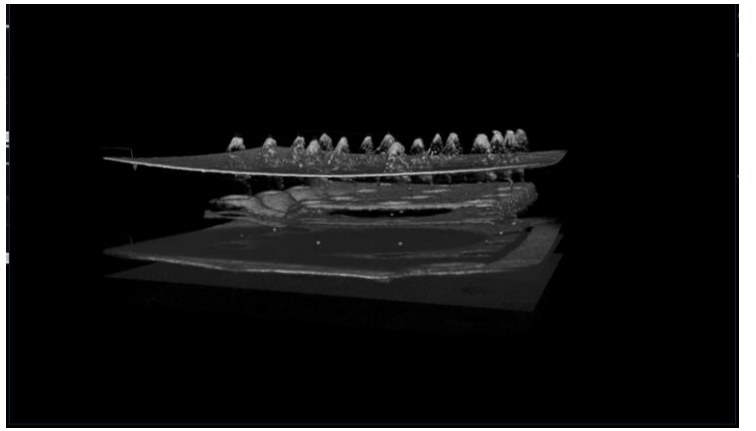




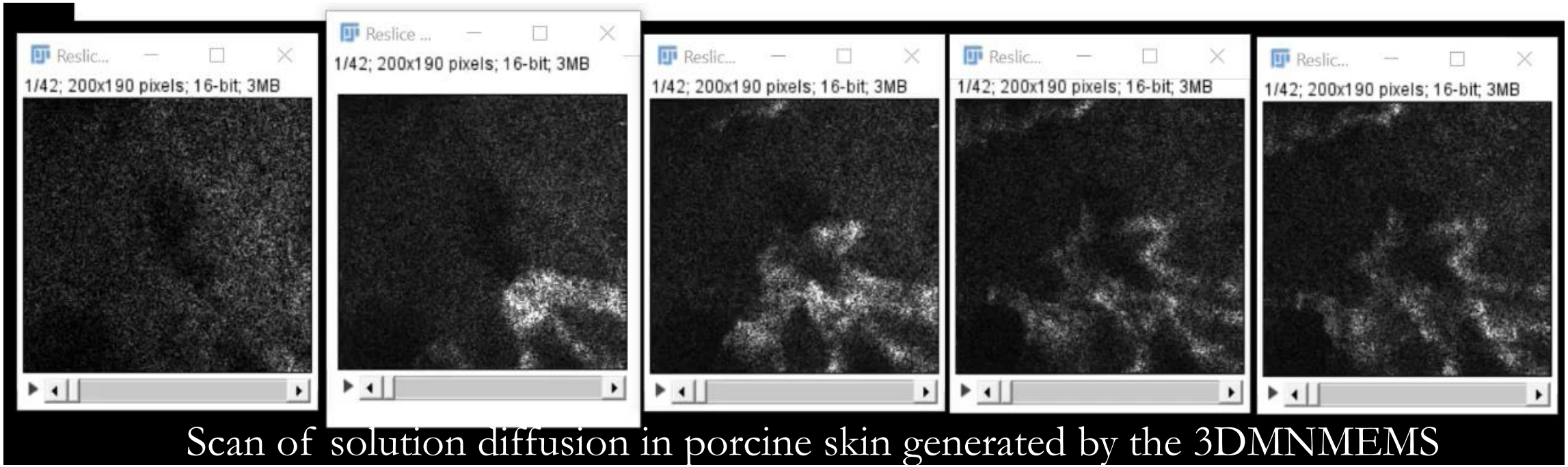
3DMNMEMS

Optical Coherence Tomography



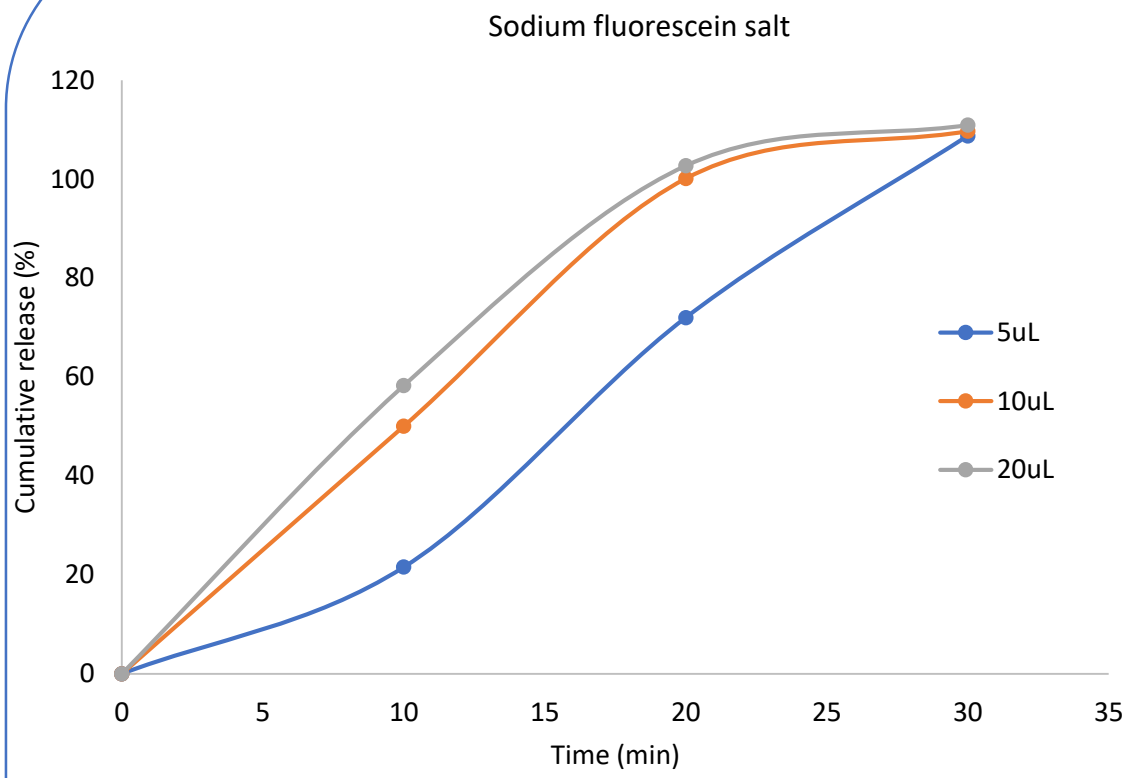


3D scanning of 3D printed MN patch

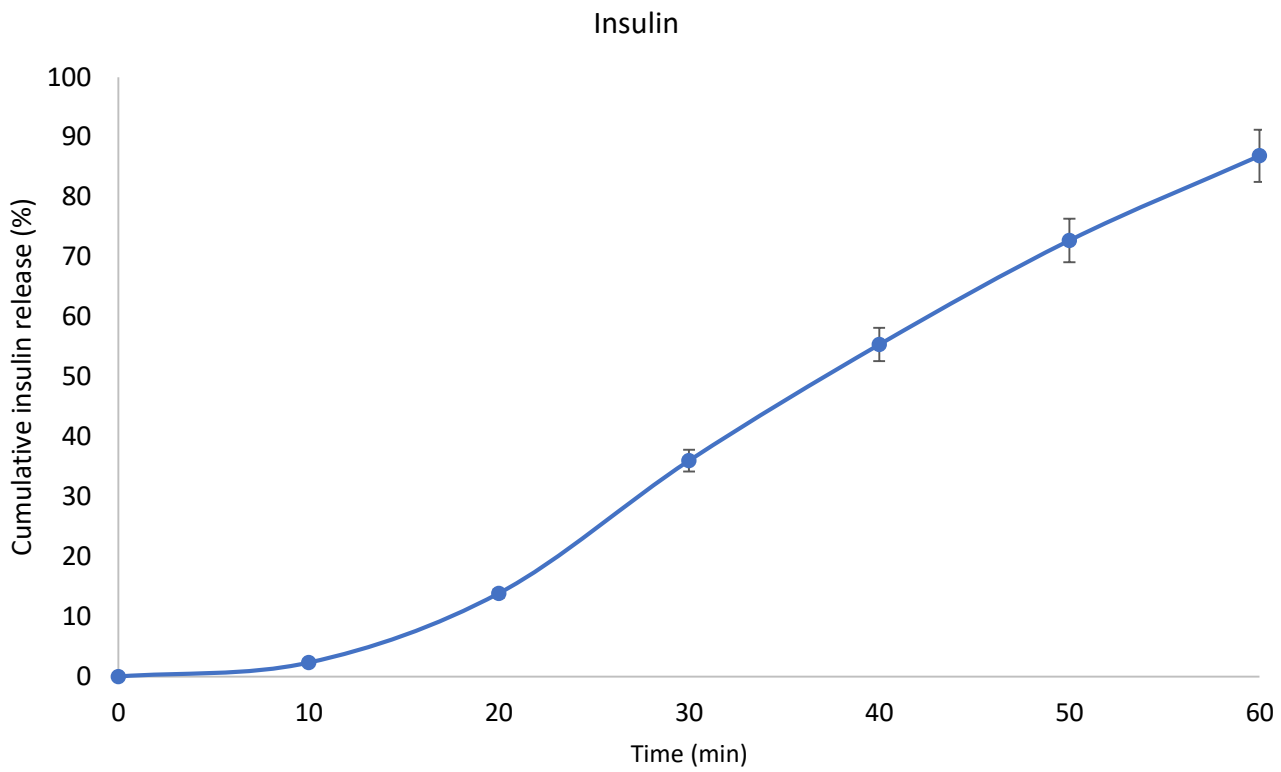


Scan of solution diffusion in porcine skin generated by the 3DMNMEMS

In vitro release studies

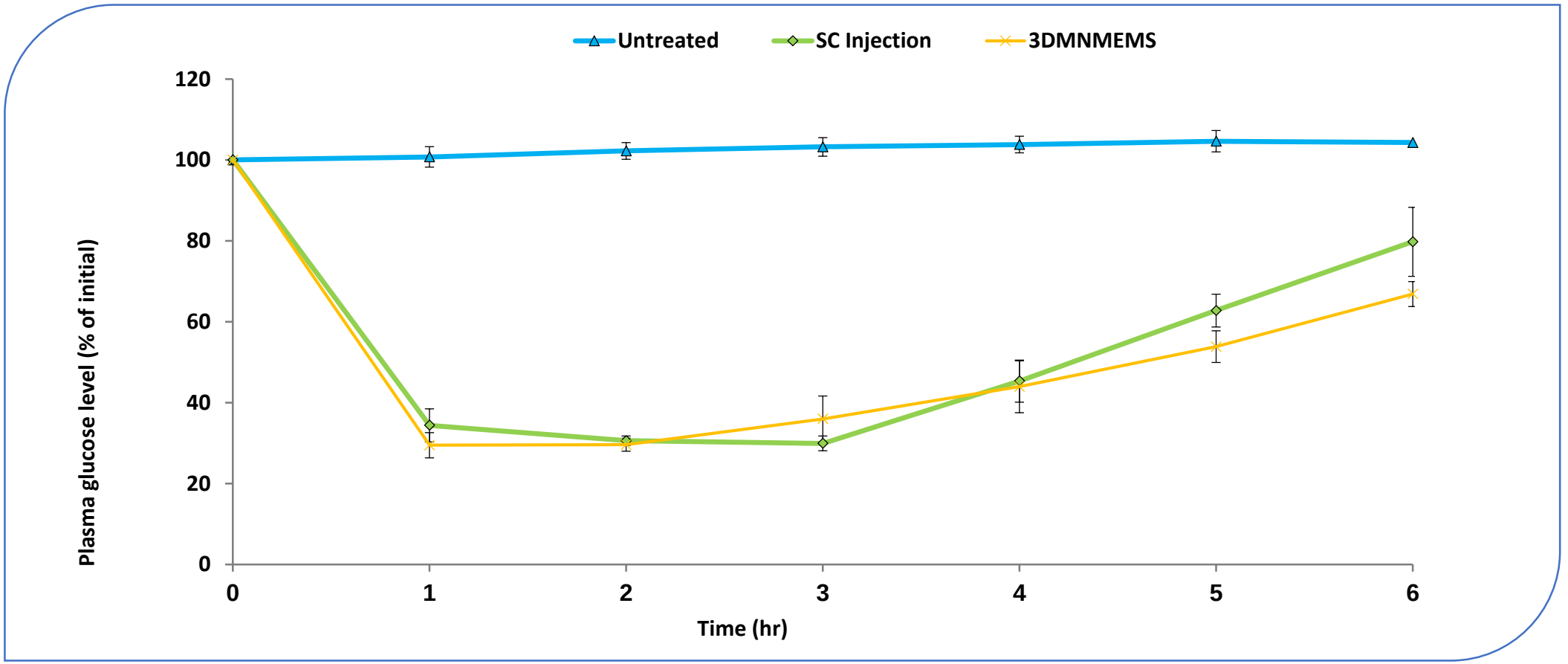


In vitro release study of sodium fluorescein salt through porcine skin using the 3DMNMEMS



In vitro release of insulin through porcine skin using the 3DMNMEMS

In vivo studies



Pharmacodynamic parameters				
	C_{min} (%)	t_{min} (h)	AAC_{0-6h}	RPA (%)
Untreated	100	0	0	0
SC	29.92106893	3	323.75	100
3DMNMEMS	29.46640994	1	340.4	105.14286

Pharmacokinetic parameters				
	C_{max} (µIU/mL)	t_{min} (h)	AUC_{0-6h}	RBA (%)
Untreated	0	0	0	0
SC	73.24	3	284.3	100
3DMNMEMS	71.6	1	274.95	96.7112

Conclusions

- ✓ Hollow MN arrays of high quality and reproducibility were successfully fabricated by stereolithography using a Class I biocompatible resin.
- ✓ The 3D printed polymeric MNs required low forces to penetrate porcine skin, in comparison to identical solid ones. The fracture forces were high compared to the piercing ones, yielding high margins of safety.
- ✓ The MNs were coupled with a MEMS, creating in a sophisticated 3DMNMEMS. OCT studies showed that solution supplied by the system diffuses in porcine skin.
- ✓ *In vivo* animal trials demonstrated that the 3DMNMEMS was able to effectively administer insulin to diabetic mice and enable rapid lowering of glucose levels.

Acknowledgements

- ✓ Dr Manuel Marques, School of Biosciences, University of Kent
- ✓ Prof. Adrian Podoleanu, School of Biosciences, University of Kent
- ✓ Dr. Md. Jasim Uddin, BRAC University, Bangladesh
- ✓ **Prof. Dennis Douroumis**, Faculty of Engineering and Sciences, University of Greenwich

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THANK YOU

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Related publications:

- Economidou SN et al. 3D printed microneedle patches using stereolithography (SLA) for intradermal insulin delivery. Mat. Sci. & Eng. C 2019, 102, 743–755.
- Pere CPP, Economidou SN et al. 3D printed microneedles for insulin skin delivery. Int J Pharm. 2018, 544(2):425-432
- Economidou SN et al. 3D printing applications for transdermal drug delivery. Int J Pharm. 2018, 544(2):415-424