Nano meets micro:
Enhanced dermal delivery of lipophilic tocotrienol nanoemulsion using microneedles

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CRS 2025 ANNUAL MEETING & EXPOSITION
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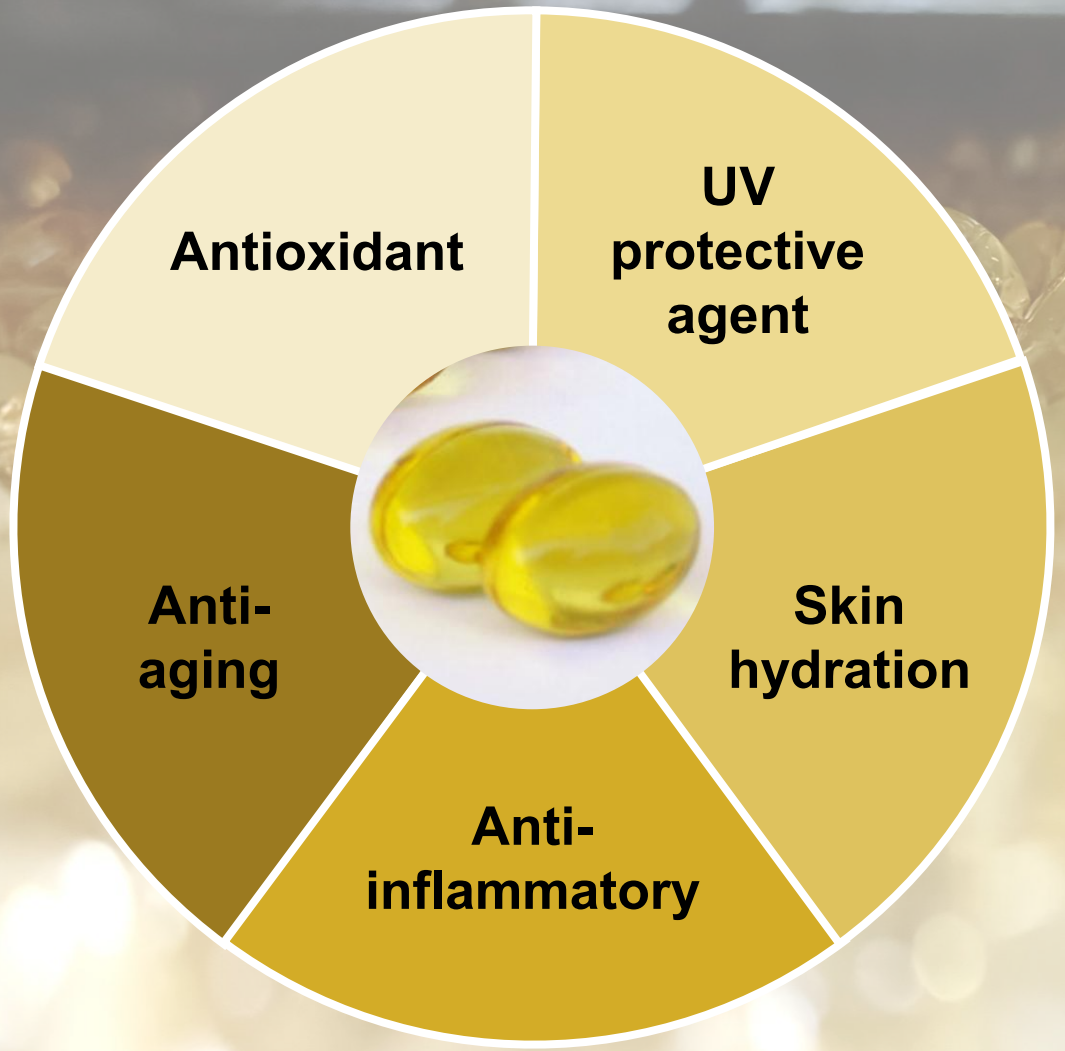
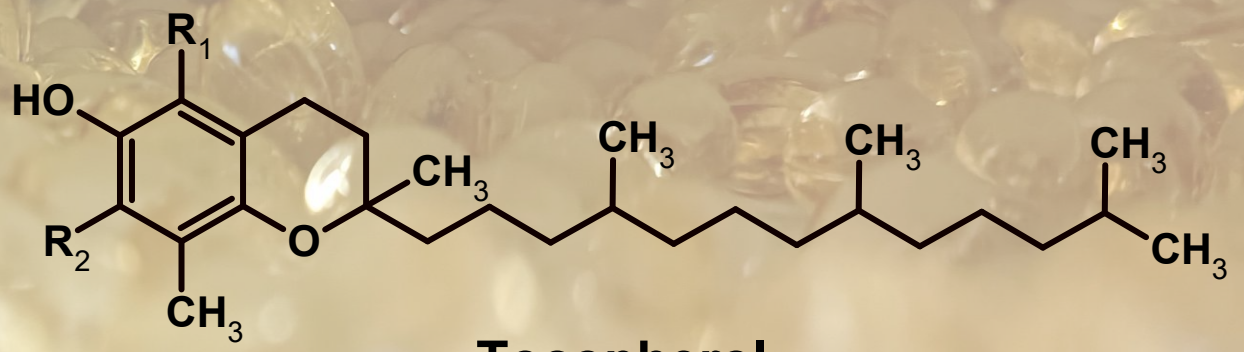
NEXT-GENERATION DELIVERY INNOVATIONS

Vitamin E

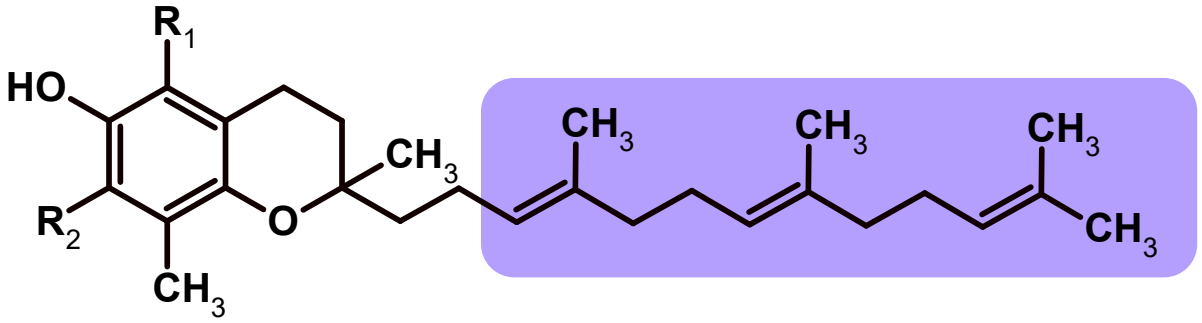




Tocopherol

Predominant form of Vitamin E
High affinity to TP transfer protein

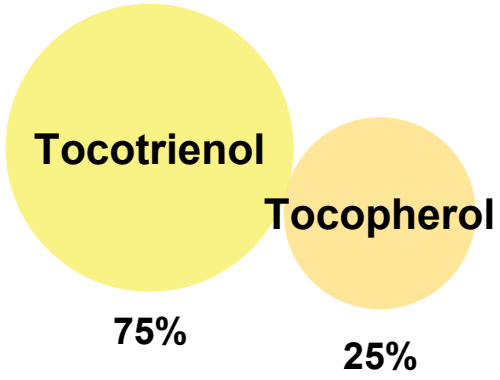
Tocotrienol (T3)



60x

antioxidant properties

Tocotrienol-rich fraction (TRF)



Challenges in individual isomer purification

Plant-based sources of T3

Palm oil

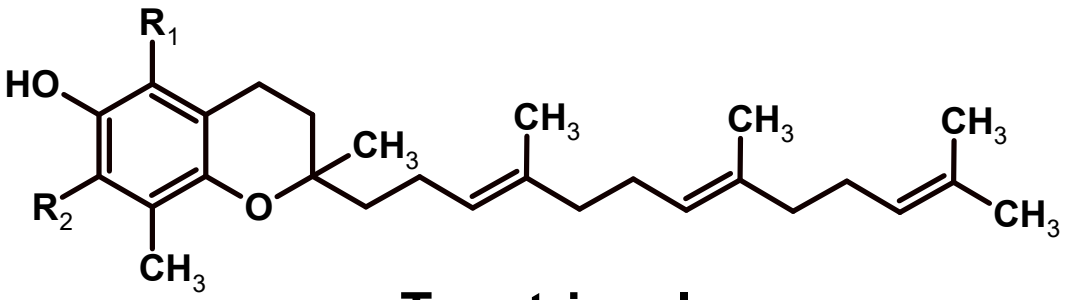
Wheat germ

Annatto

Barley

Malaysia as the 2nd largest palm oil exporter in the world

Dermal health benefits



Tocotrienol

Anti-aging
UV protective
Anti-inflammatory

Skin moisture & pigmentation

Improve skin hydration with melanin index reduction in humans

J. Dispers. Sci. Technol., 30(1), 72-75

Photoprotective

Photoprotective effect in individuals with photosensitivity clinical history

J. Eur. Acad. Dermatol. Venereol., 26(11), 1449-1453

Anti-inflammatory

Reduced C-reactive protein and interleukin-6 level in chronic haemodialysis patients

Vasc. Health risk manag., 747-761

Physical and chemical properties

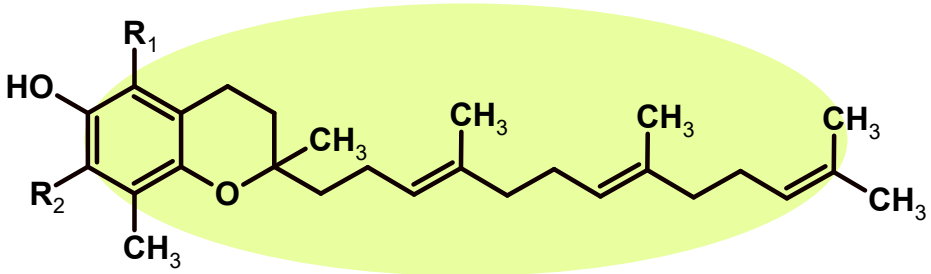
Molecular size

411 Da

Lipophilicity

Partition coefficient

log P: ~8



Tocotrienol

Ionisation & permeant binding

Hydrogen bond donor: 1

Hydrogen bond acceptor: 2

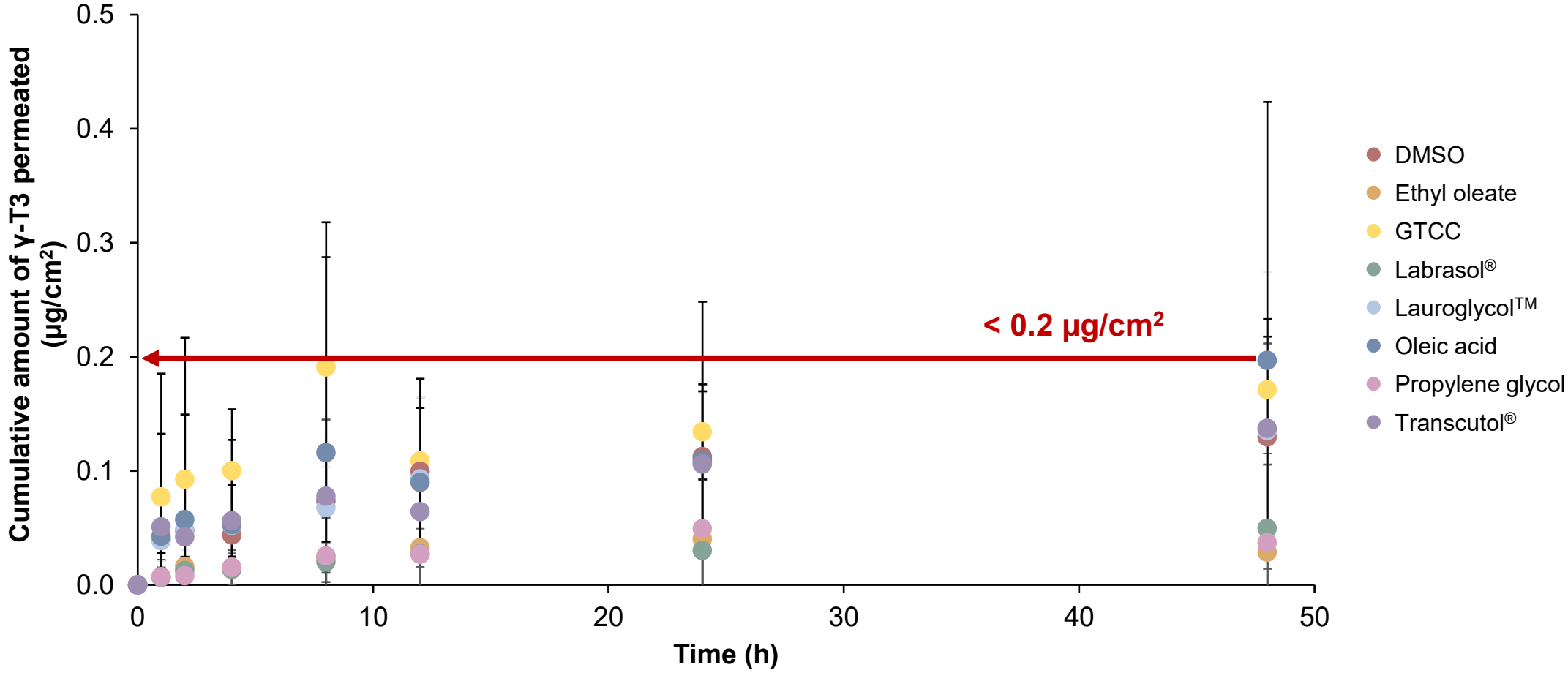
Melting point

~35°C

Malaysian Palm Oil Board. Physical properties of palm oil, https://palmoilis.mpob.gov.my/publications/POEB/poeb106-data.pdf. Accessed June 25, 2025
National Center for Biotechnology Information. PubChem compound summary for CID 5282349, Gamma-Tocotrienol. https://pubchem.ncbi.nlm.nih.gov/compound/Gamma-Tocotrienol. Accessed June 24, 2025
Tan, C.-P., Nehdi, I.A., 2012. 13 - The physicochemical properties of palm oil and its components, in: Lai, O.-M., Tan, C.-P., Akoh, C.C. (Eds.), Palm Oil. AOCS Press, pp. 377-391.

In vitro permeation study* with different solvents

Infinite dosing (10%w/v TRF)



* Porcine ear skin was used

GTCC: Caprylic/capric glyceride; Lauroglycol™: Propylene glycol monolaurate (Type III); Transcutol®: Diethylene glycol monoethyl ether; Labrasol®: PEG-8 caprylic/capric glyceride

Mass balance studies

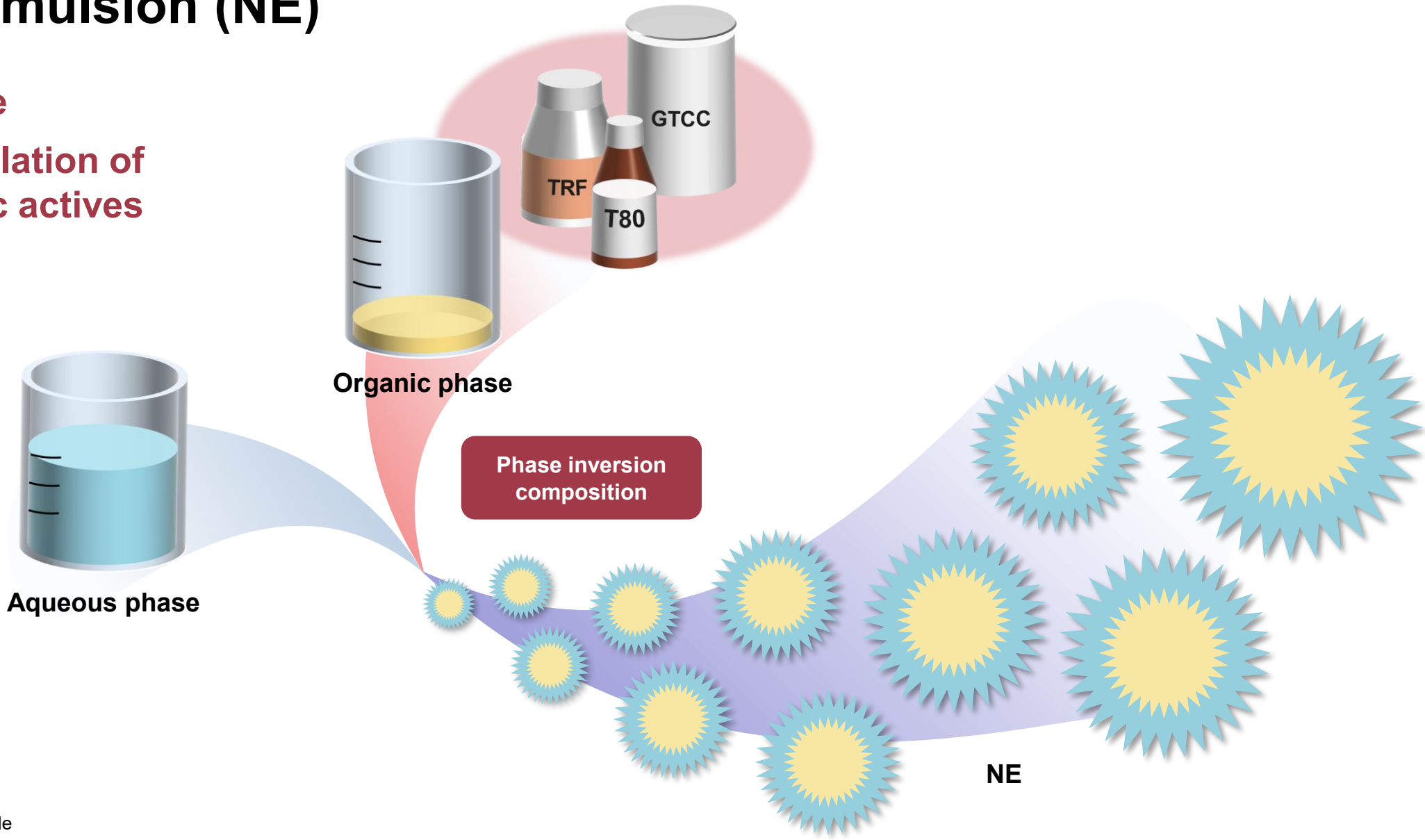
Solvents	Permeation		On skin (%)	In skin (%)	Total percentage (%)
	µg/cm²	%			
DMSO	0.130 ± 0.083	0.0058 ± 0.01	70.24 ± 15.27	0.10 ± 0.03	70.33 ± 15.29
Ethyl oleate	0.029 ± 0.015	0.0026 ± 0.01	106.58 ± 5.79	0.18 ± 0.12	106.75 ± 5.73
GTCC	0.172 ± 0.047	0.0074 ± 0.01	87.08 ± 6.99	0.02 ± 0.01	87.11 ± 6.98
Labrasol®	0.050 ± 0.066	0.0022 ± 0.01	106.95 ± 14.99	0.04 ± 0.01	106.99 ± 15
Lauroglycol™	0.136 ± 0.14	0.0076 ± 0.01	125.52 ± 11.12	0.03 ± 0.01	125.56 ± 11.12
Oleic acid	0.197 ± 0.227	0.0055 ± 0.01	78.19 ± 5.04	0.03 ± 0.01	78.22 ± 5.03
Propylene glycol	0.038 ± 0.069	0.0159 ± 0.02	102.89 ± 5	0.88 ± 0.28	103.78 ± 4.87
Transcutol®	0.138 ± 0.096	0.0054 ± 0.01	97.8 ± 2.46	0.07 ± 0.02	97.87 ± 2.44

< 0.02%

Nanoemulsion (NE)

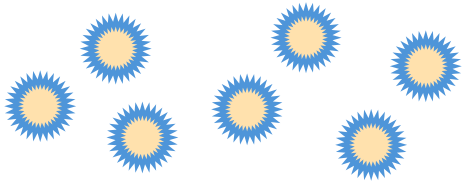
Nanosize

Encapsulation of lipophilic actives



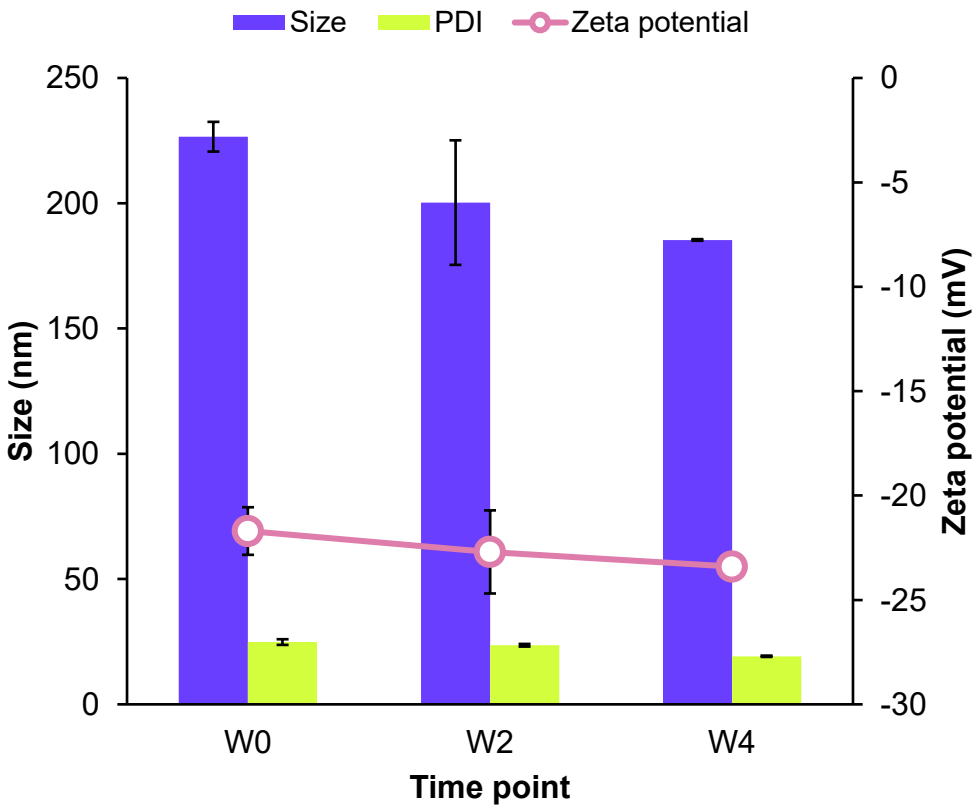
GTCC: Caprylic/capric glyceride
NE: Nanoemulsion
T80: Tween® 80

Chracterisation of TRF-loaded NE



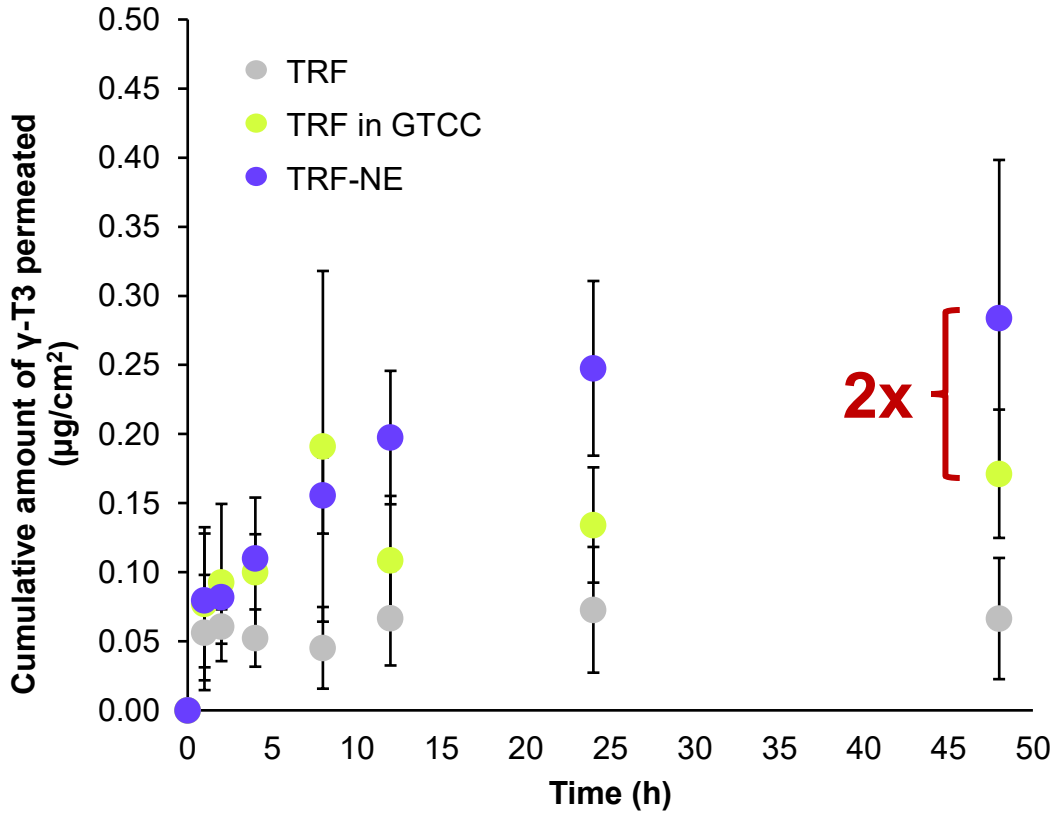
- TRF
- GTCC
- T80

Stability study



In vitro permeation study*

TRF:	TRF in GTCC:	TRF-loaded NE:
Infinite	Infinite (10%w/v TRF)	Infinite (8%w/v TRF)
Dose: ~15 mg/cm^2	Dose: ~2 mg/cm^2	Dose: ~1.5 mg/cm^2



* Porcine ear skin was used

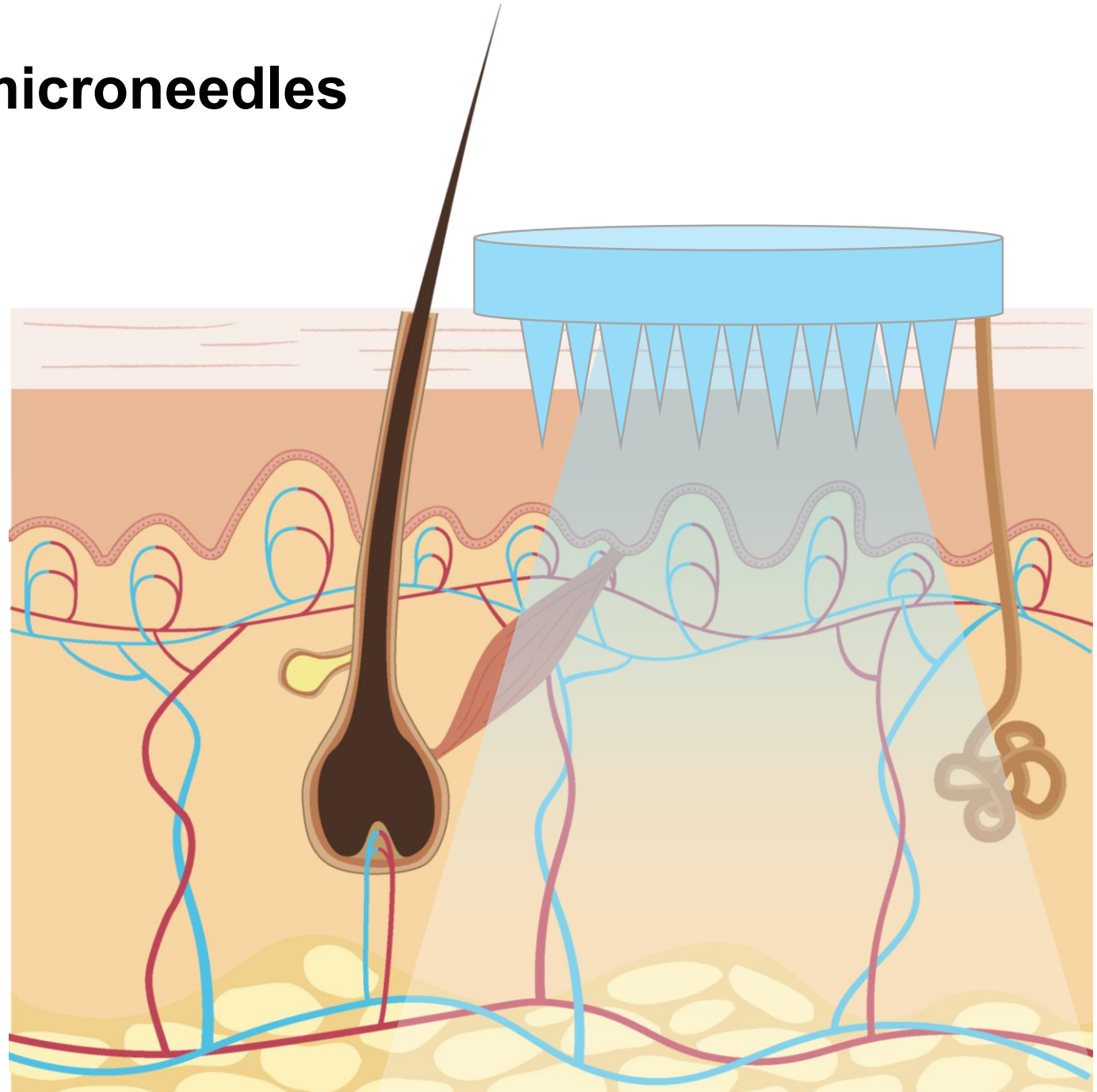
Recent literature on TRF nanoformulations

	Current work	Harun et al., 2021	Nair et al., 2021	Pham et al., 2014
Nanoformulation	Nanoemulsions	Nanoemulsions	Ethosomes	Nanoemulsions
Dose (mg)	1	4	1	7
Membrane used	Full thickness porcine skin	Rat skin	Full thickness human skin	Artificial cellulose-ester membrane
Cumulative amount of γ-T3 permeated (μg/cm²)	~0.3	NA	~1	~2
Cumulative amount of γ-T3 permeated (%)	~0.05	~25	0.1	~0.03

< 1% permeated

Harun, M.S., Wong, T.W., Fong, C.W., 2021. Advancing skin delivery of α-tocopherol and γ-tocotrienol for dermatitis treatment via nanotechnology and microwave technology. International Journal of Pharmaceutics 593, 120099.
Nair, R.S., Billa, N., Leong, C.O., Morris, A.P., 2021. An evaluation of tocotrienol ethosomes for transdermal delivery using Strat-M® membrane and excised human skin. Pharmaceutical Development and Technology 26, 243-251.
Pham, J., Nayel, A., Hoang, C., Elbayoumi, T., 2016. Enhanced effectiveness of tocotrienol-based nano-emulsified system for topical delivery against skin carcinomas. Drug Delivery 23, 1514-1524.

Dissolving microneedles

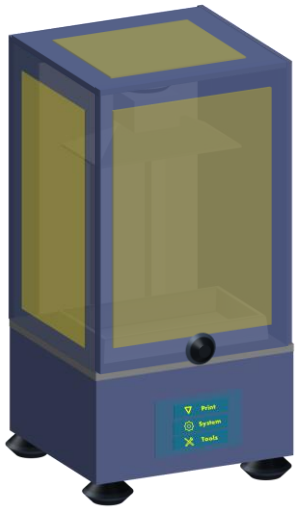


3D printing

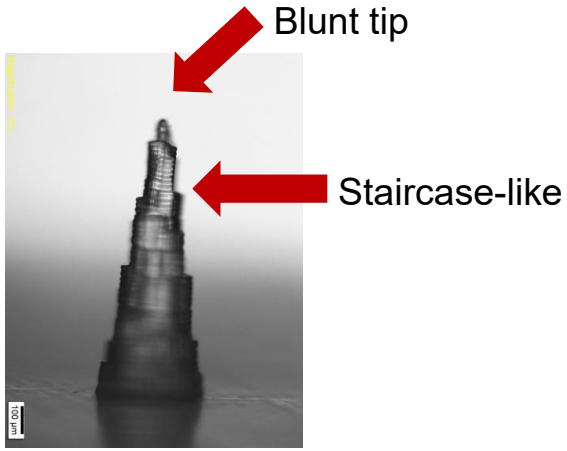
Customisable designs

Tune MN dimensions

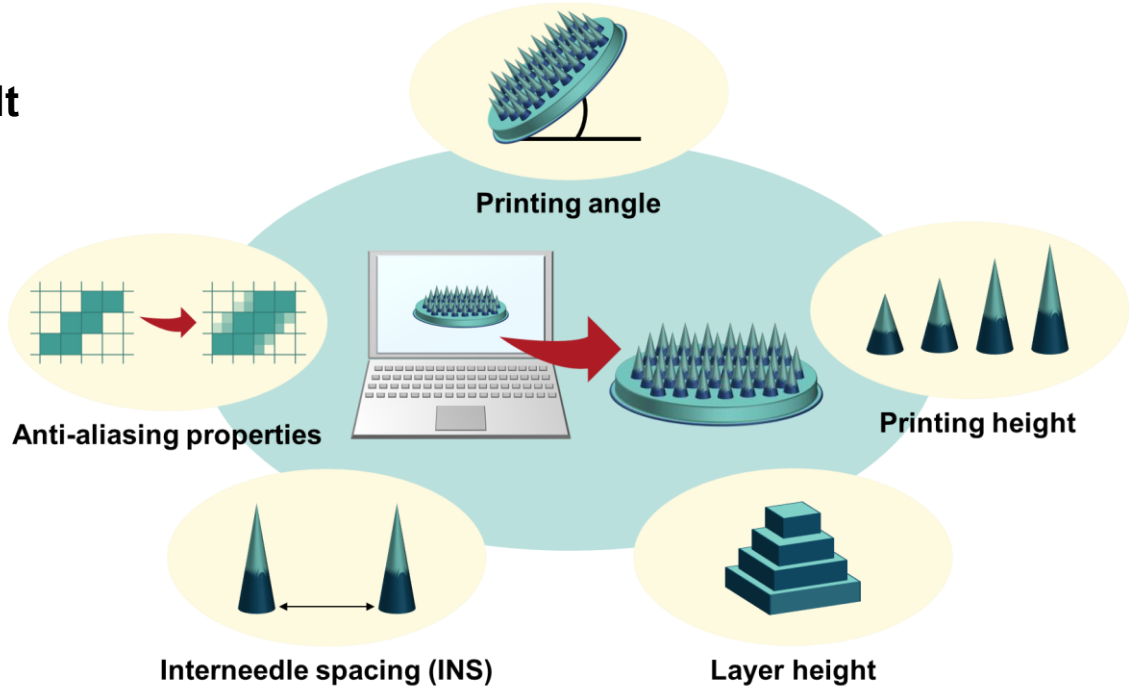
Number of needles



Low cost conventional 3D printer

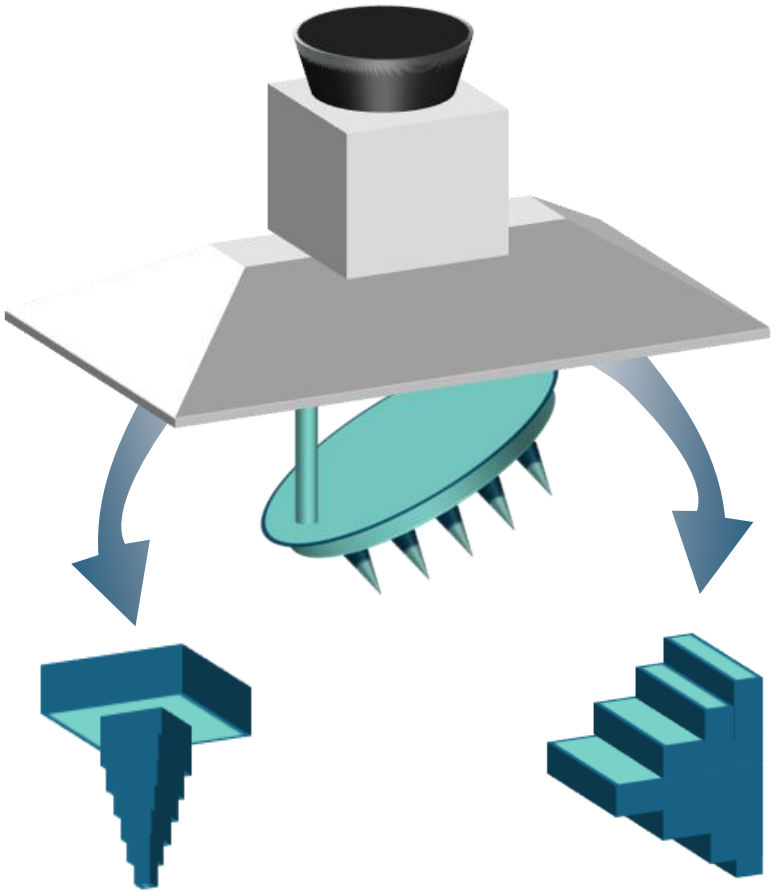


MN printed at default print setting



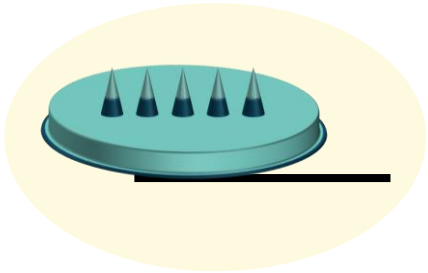
Printing parameters

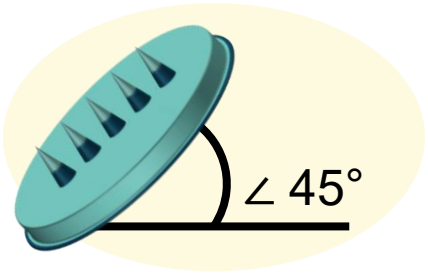
Printing angle

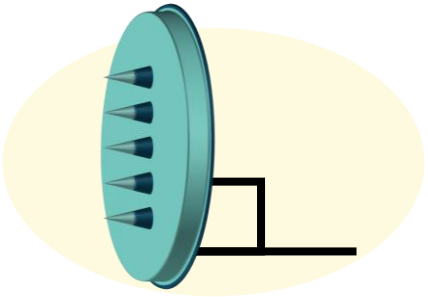


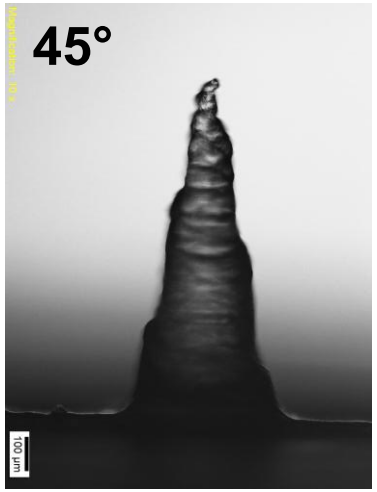
∠ 0°

∠ 90°







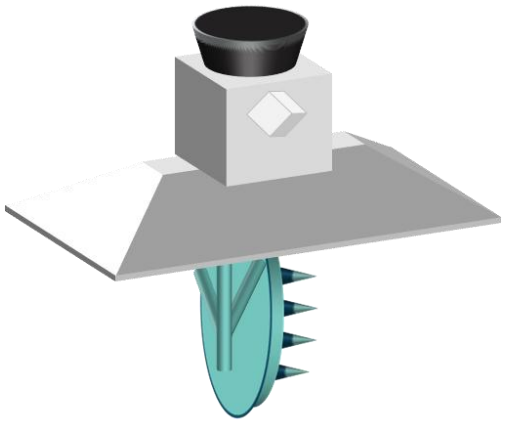


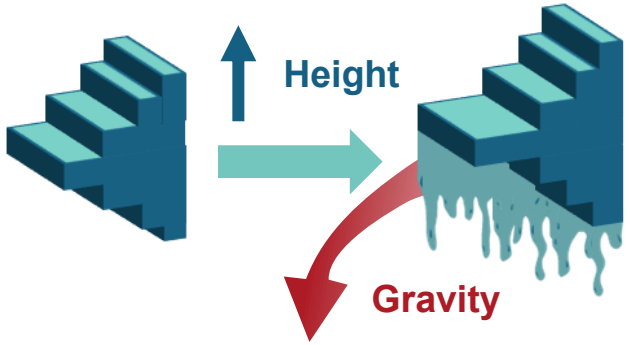
Staircase effect

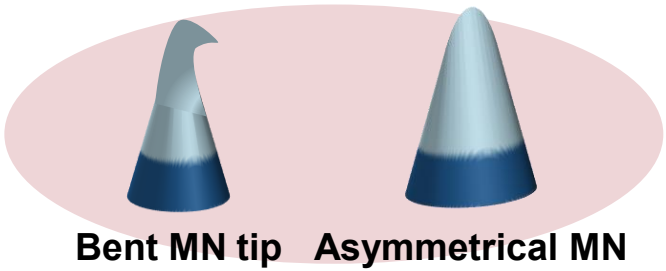
Layer-by-layer curing pattern

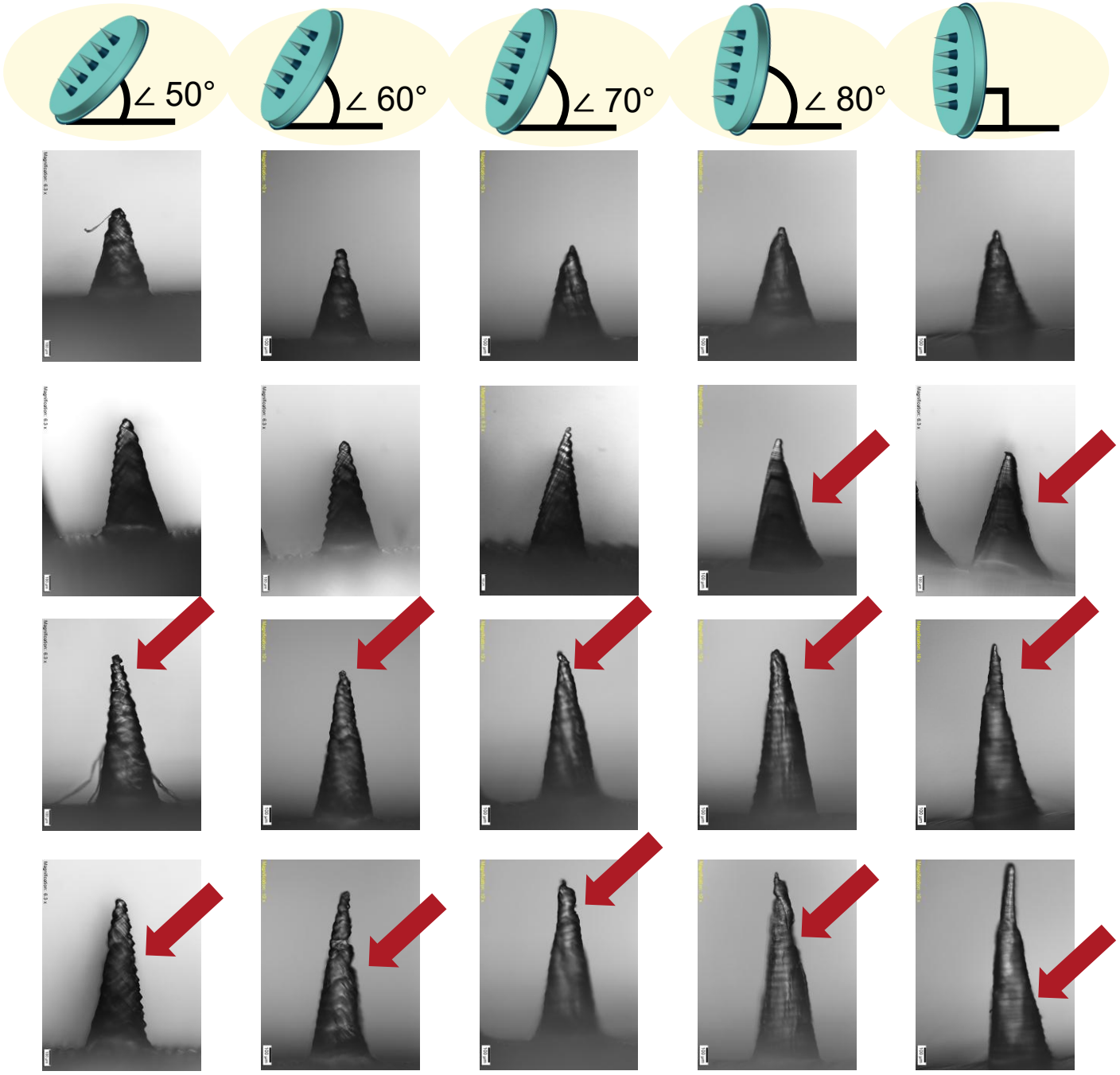
Ensure better functionality of MN

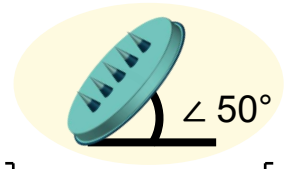
Printing height

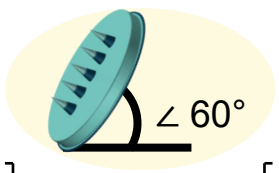


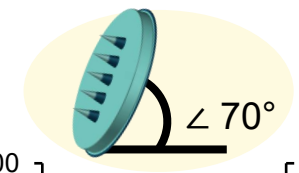


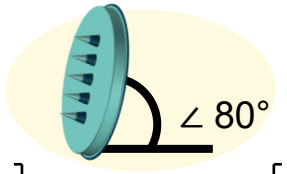


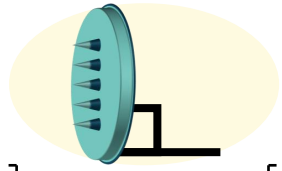


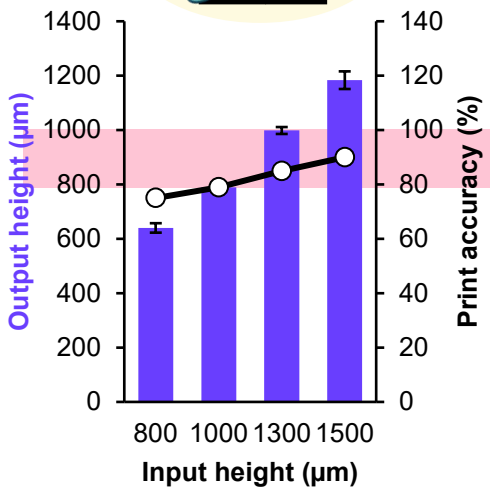


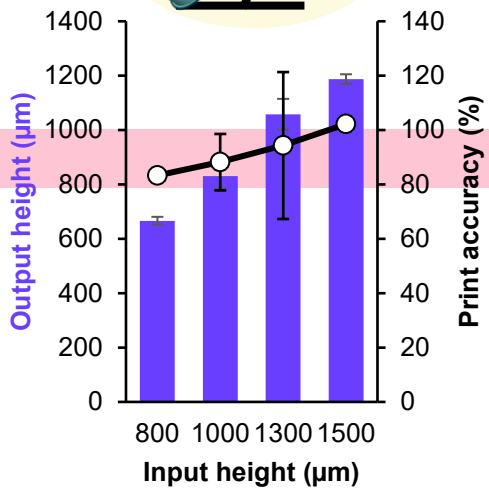


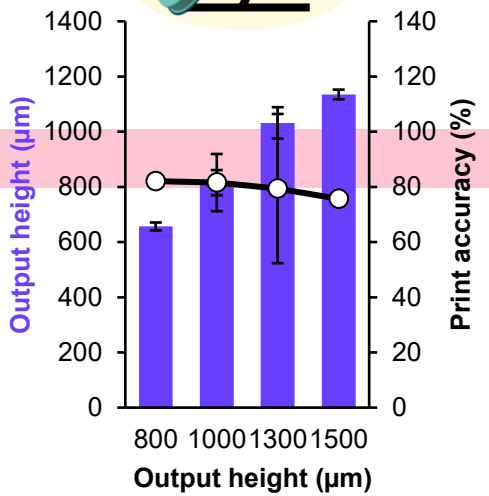


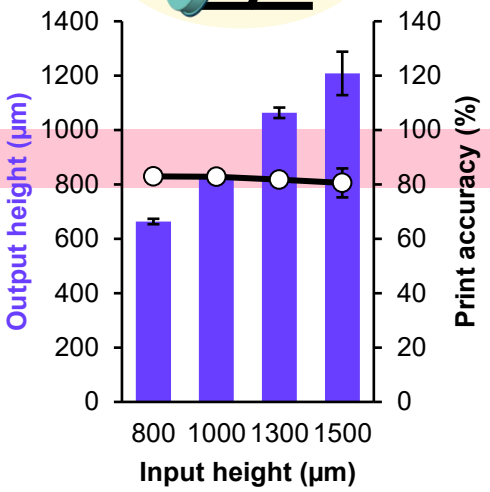


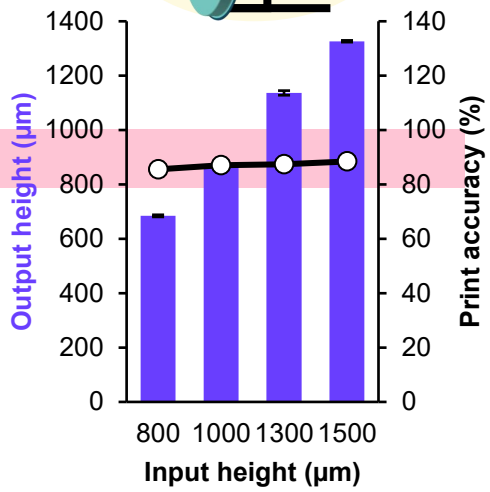








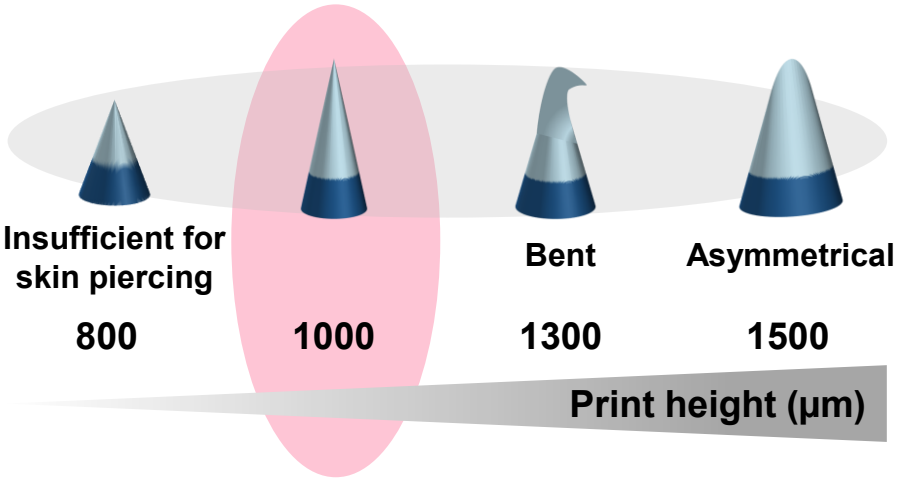


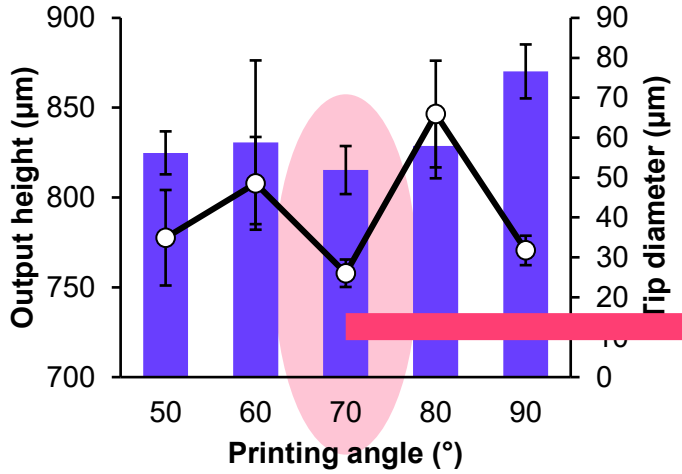


$$Print\ accuracy\ (\%) = \frac{Output\ height\ (\mu m)}{Input\ height\ (\mu m)} \times 100\%$$

Output height — Print accuracy

> 80% print accuracy





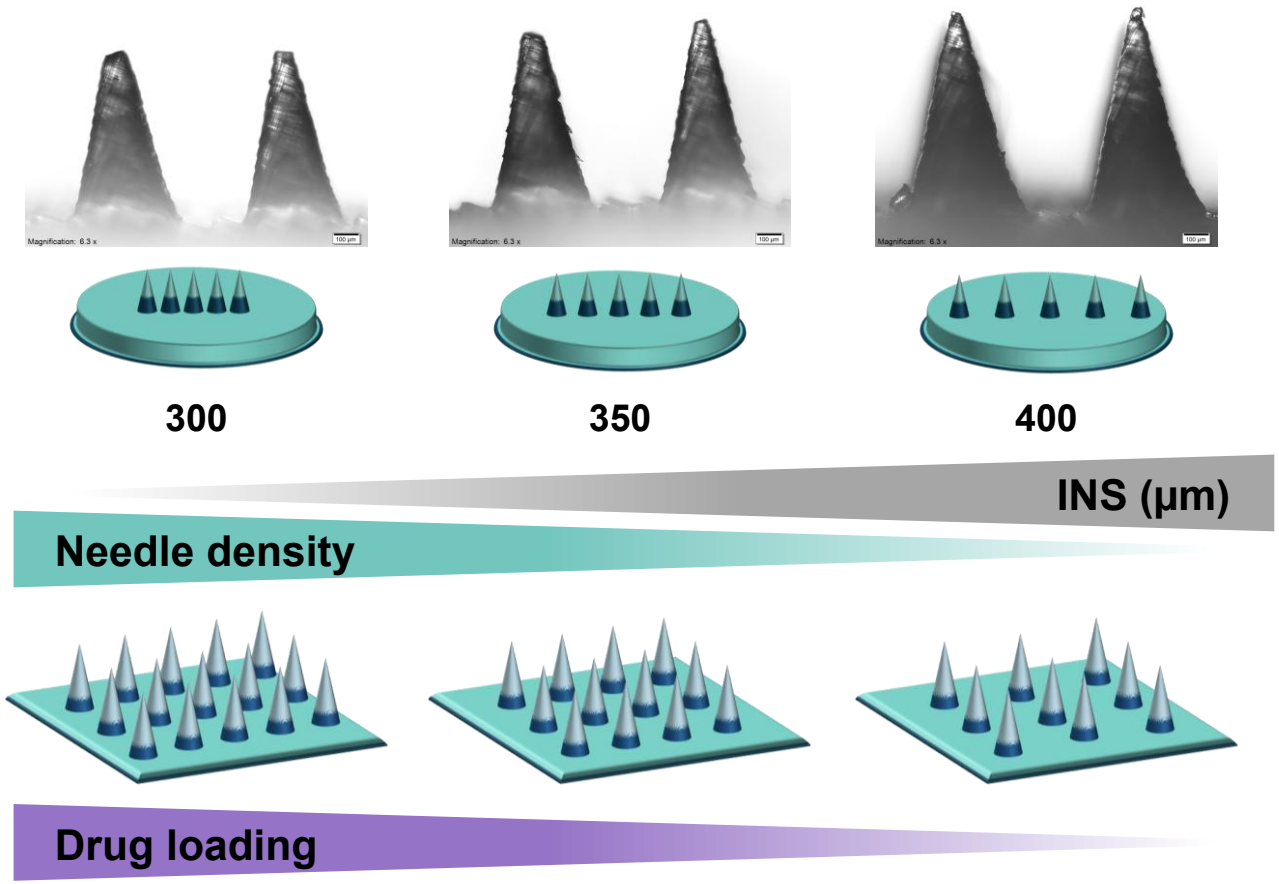
Smallest tip diameter (~26 μm)

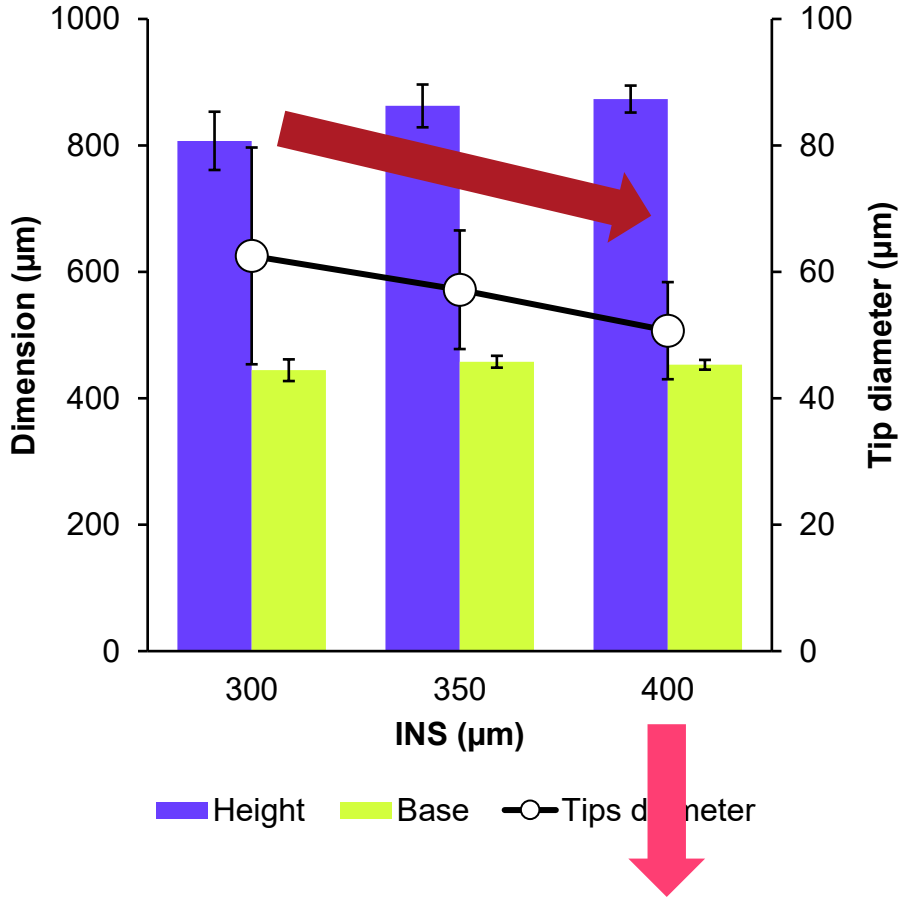
Output height — Tip diameter

Mean ± SD; n = 30

Interneedle spacing (INS)

Distance between edge of neighbouring needles





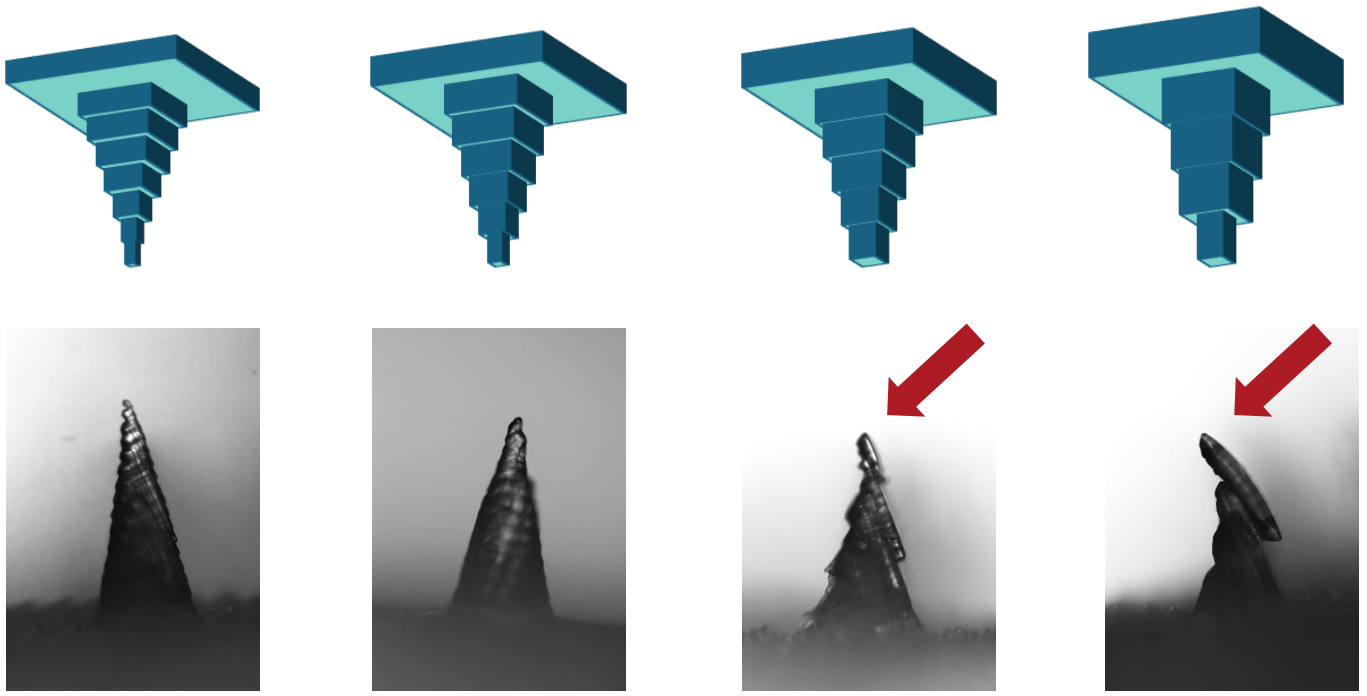
‘Bed of nail’ phenomenon

Insertion force

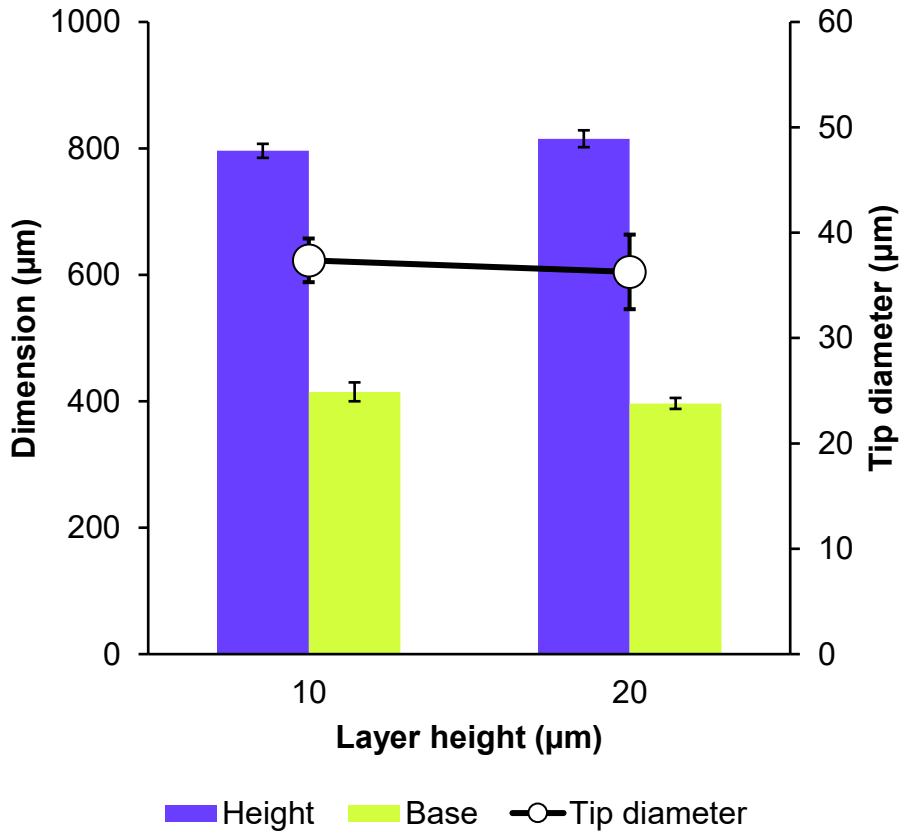
Reduce ‘bed of nail’ effect

Mean ± SD; n = 30

Layer height



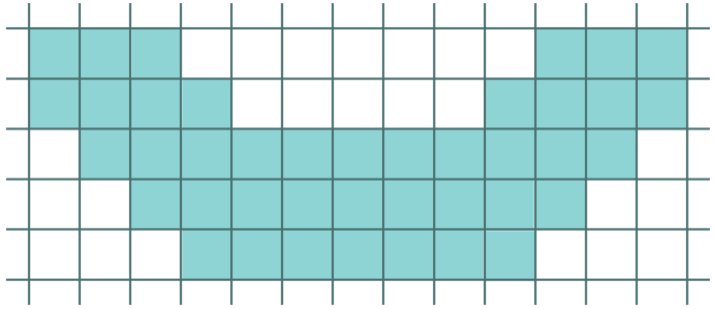
Smoother surface finish



Mean ± SD; n = 30

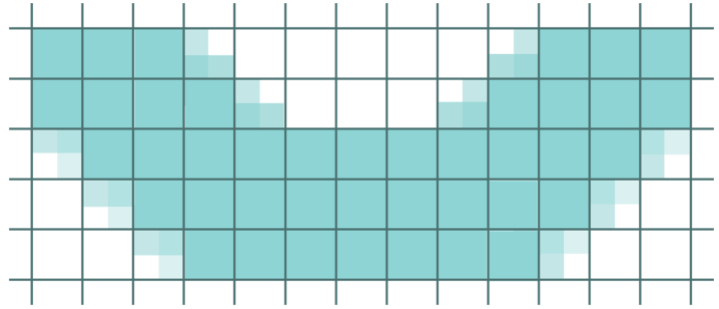
Anti-aliasing

Digital signal processing technique

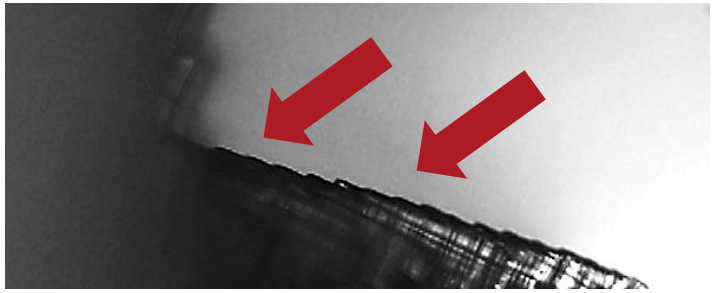


Aliased

Blurring and grayscale level

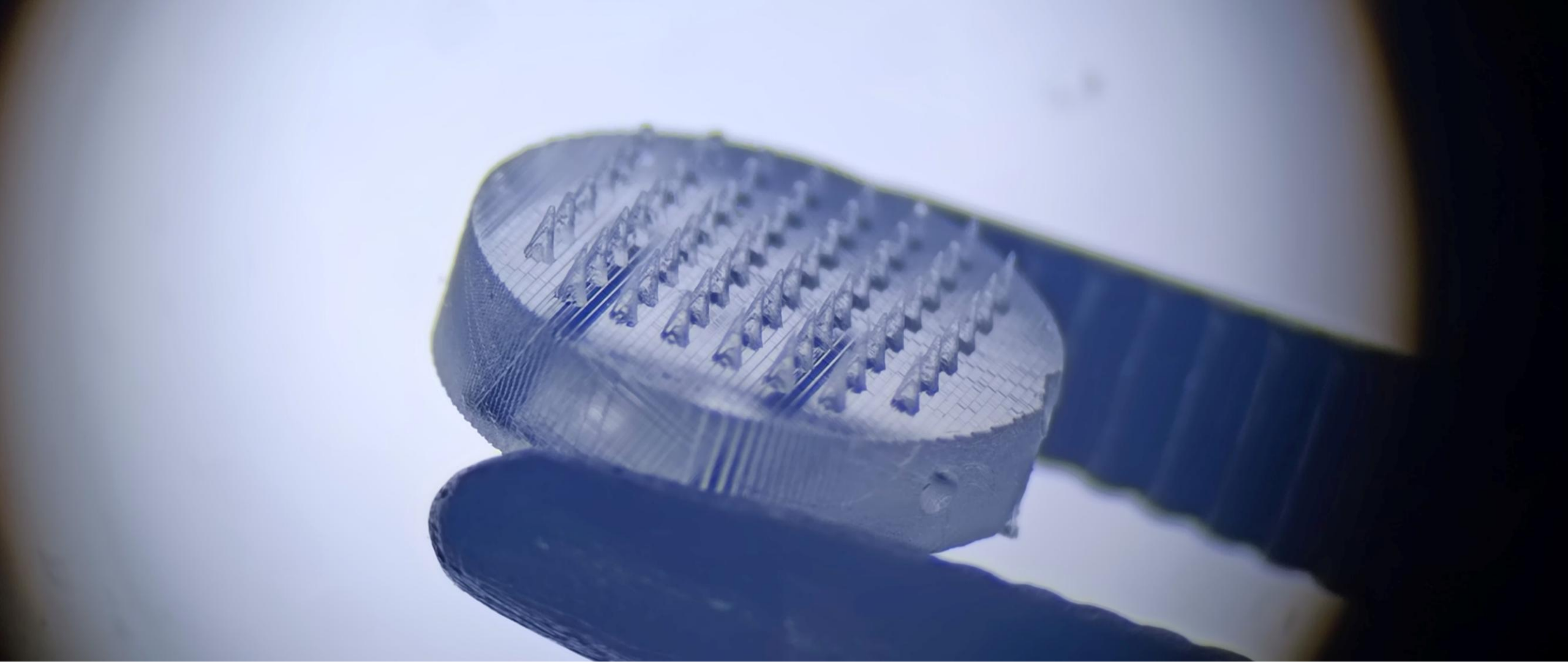


Anti-aliased



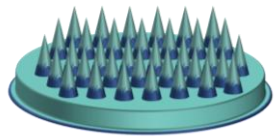
Jagged surface

Smooth surface

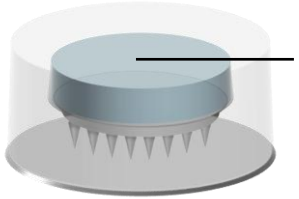


Printing angle	70°	**INS**	400 µm
Printing height	1000 µm	**Anti-aliasing**	On
Layer height	10 µm	**Number of needles**	60 conical needles

Validation of 3DP MN



Optimised 3DP MN



- **PVA**
- **Caffeine as a model drug***

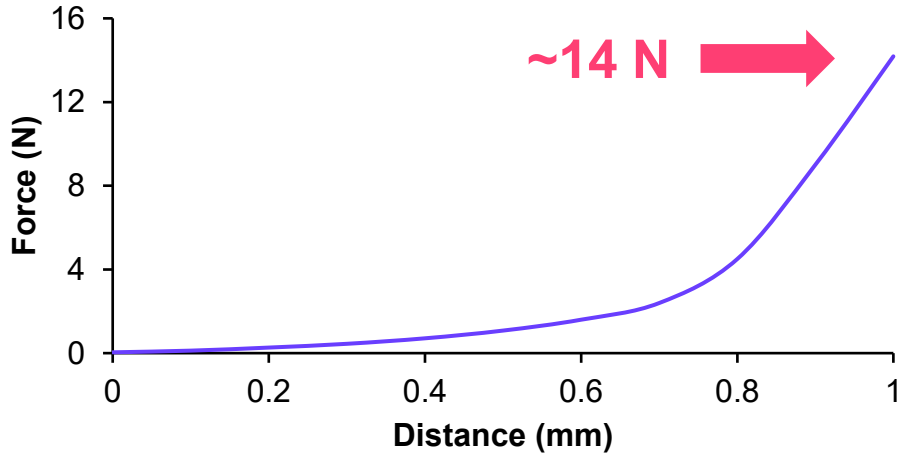
PDMS mould

Caffeine-loaded DMN (CAF-DMN)

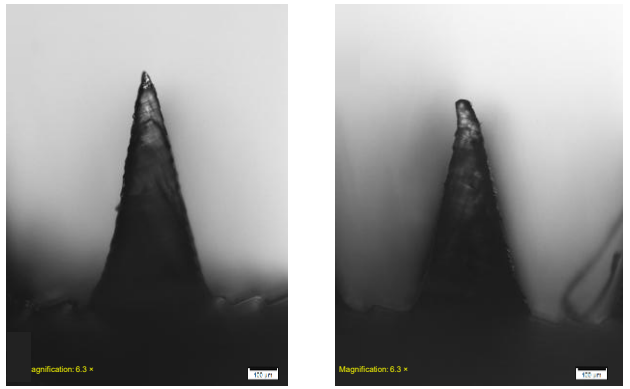
Height	**807.34 ± 14.96 µm**
Base	**417.08 ± 9.17 µm**
Tip diameter	**38.86 ± 7.82 µm**

Mechanical properties

Axial compression test



Percentage MN height reduction test

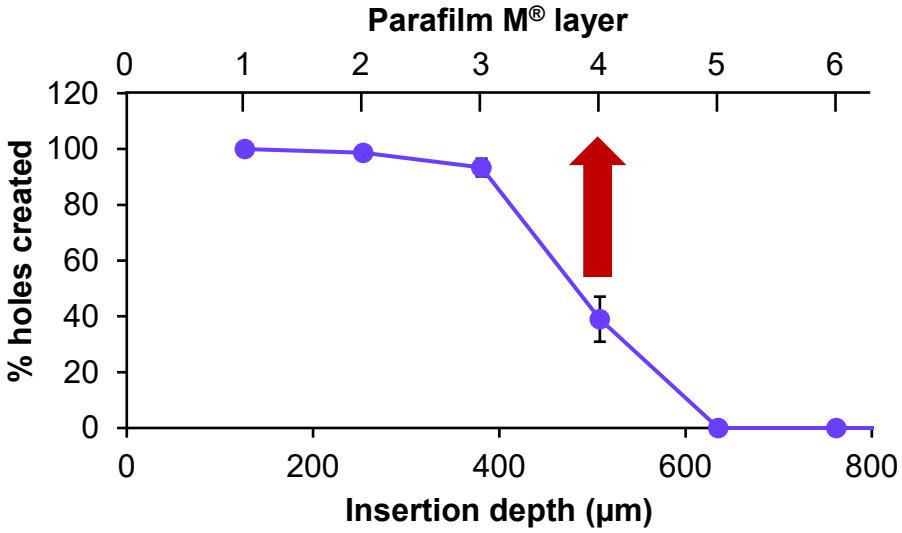


~6%

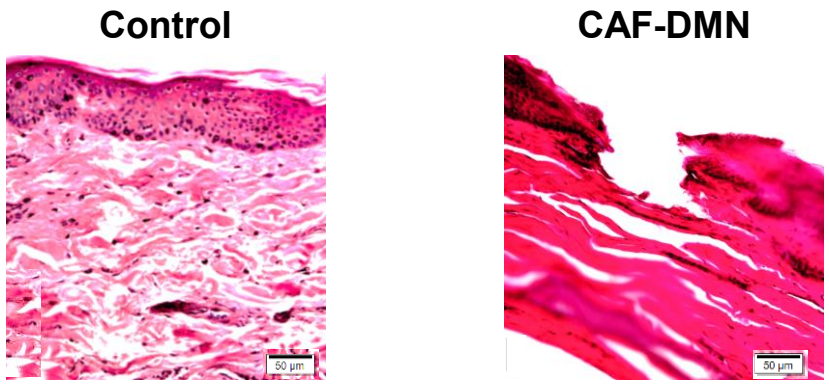
* Ease of incorporation into hydrophilic PVA matrix; established studies available on caffeine-loaded MNs

Insertion profiles

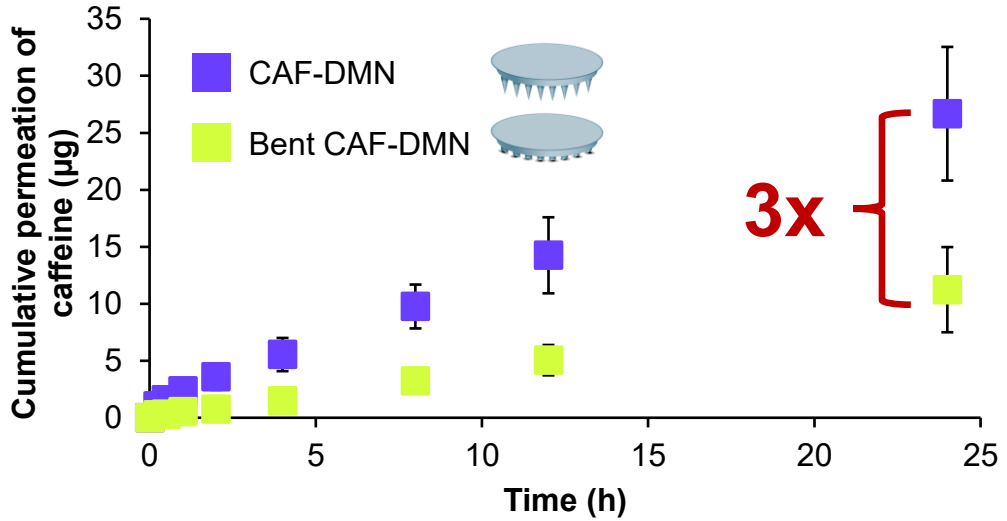
Parafilm® M insertion test

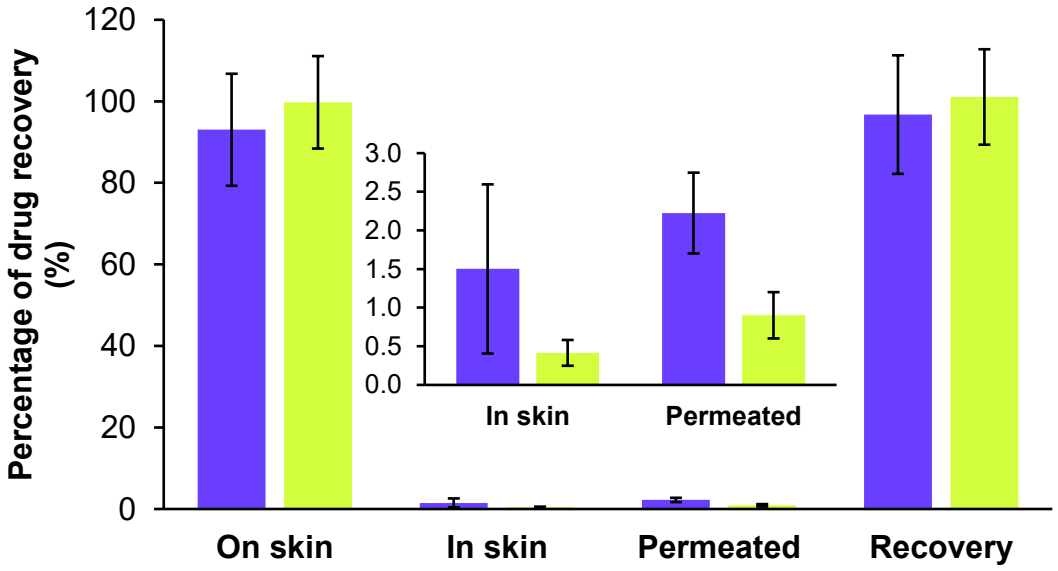


In vitro skin insertion test*



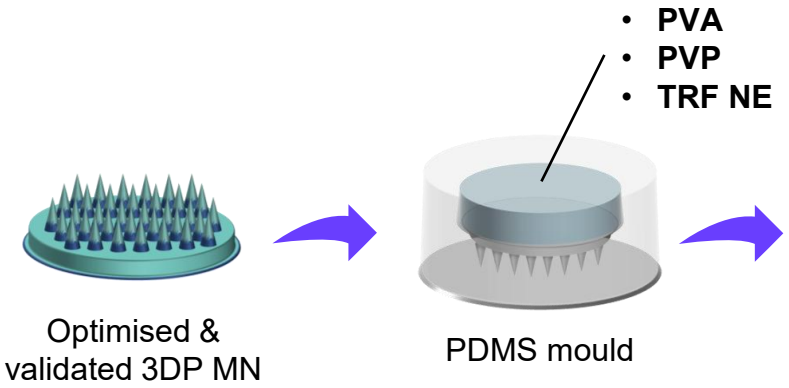
In vitro permeation* and mass balance studies of CAF-DMN

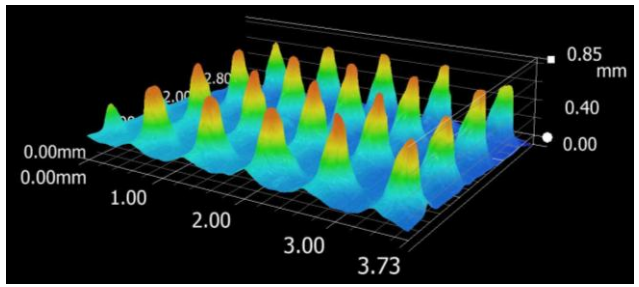




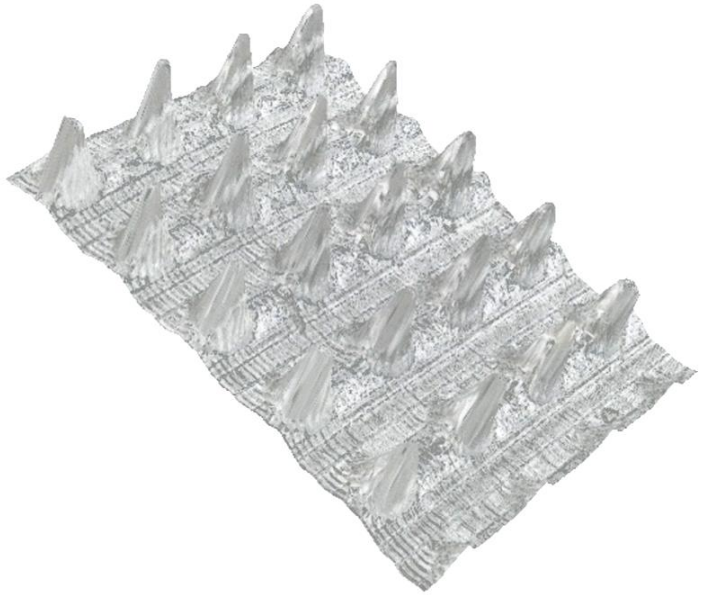
* Porcine ear skin was used

TRF NE-loaded MN



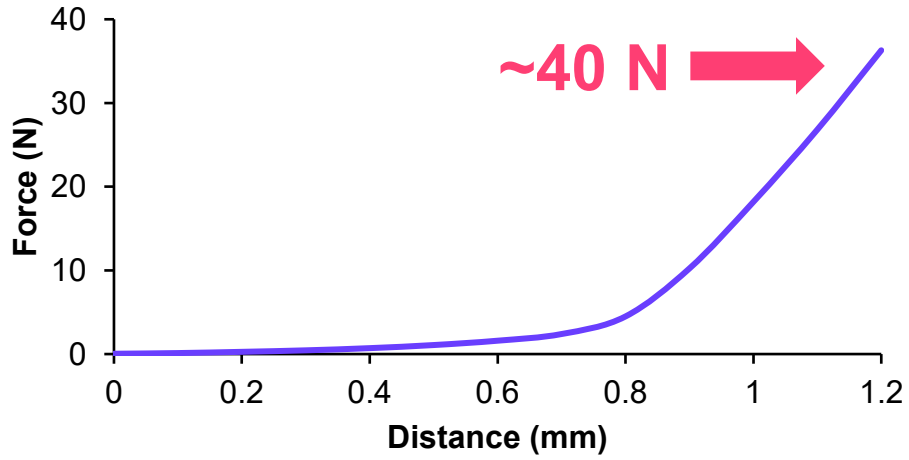


TRF NE-MN

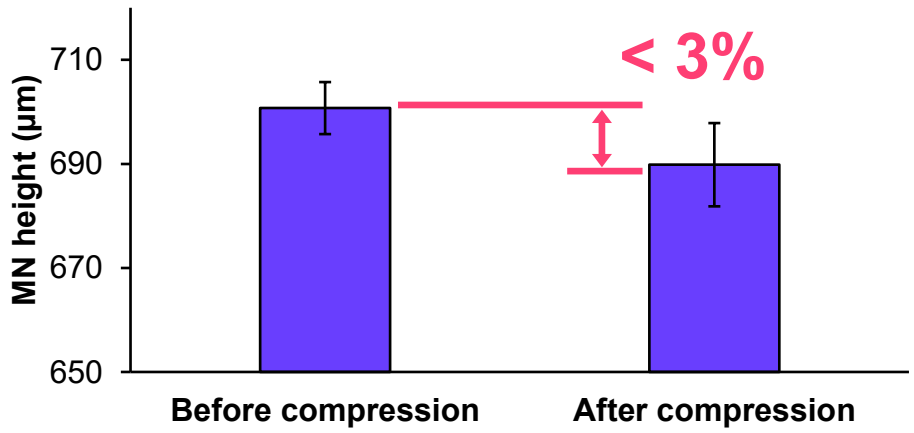


Mechanical properties

Axial compression test

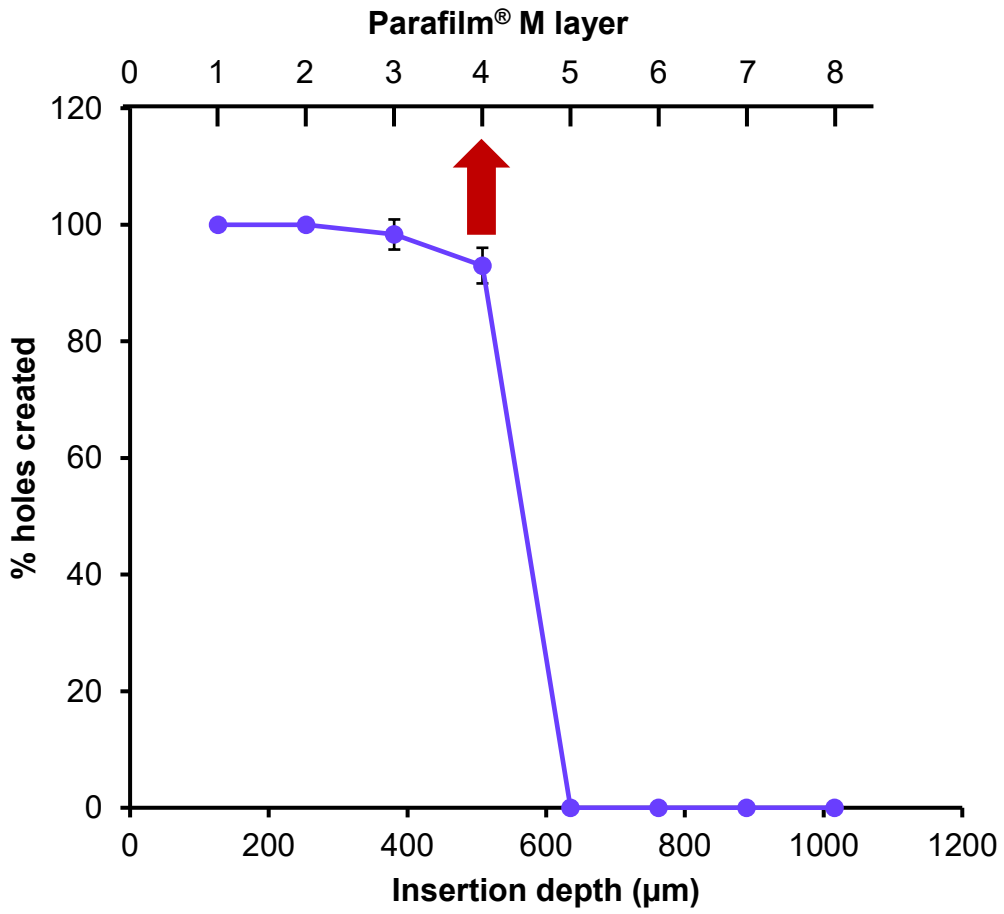


Percentage MN height reduction test

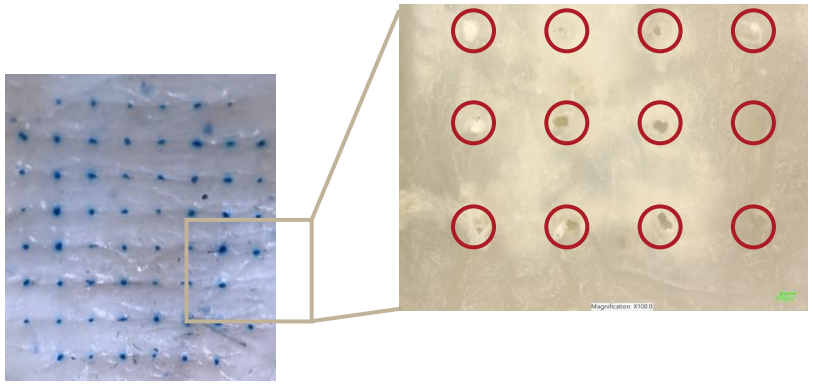


Insertion profiles

Parafilm® M insertion test

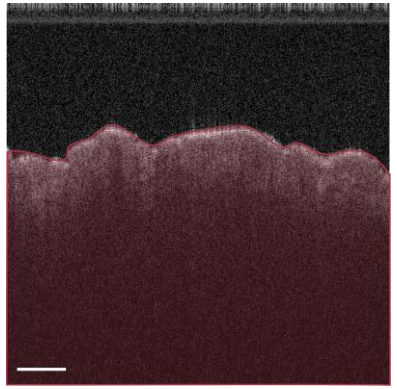


In vitro skin insertion test*



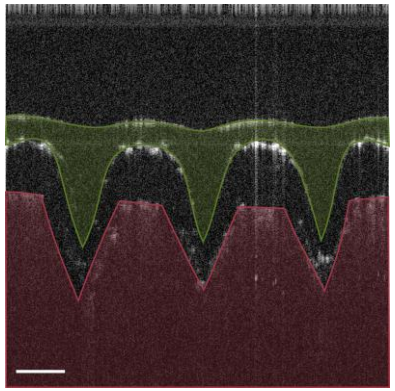
89 ± 2.01%

Control



Penetration depth

TRF NE-loaded MN



~400 µm

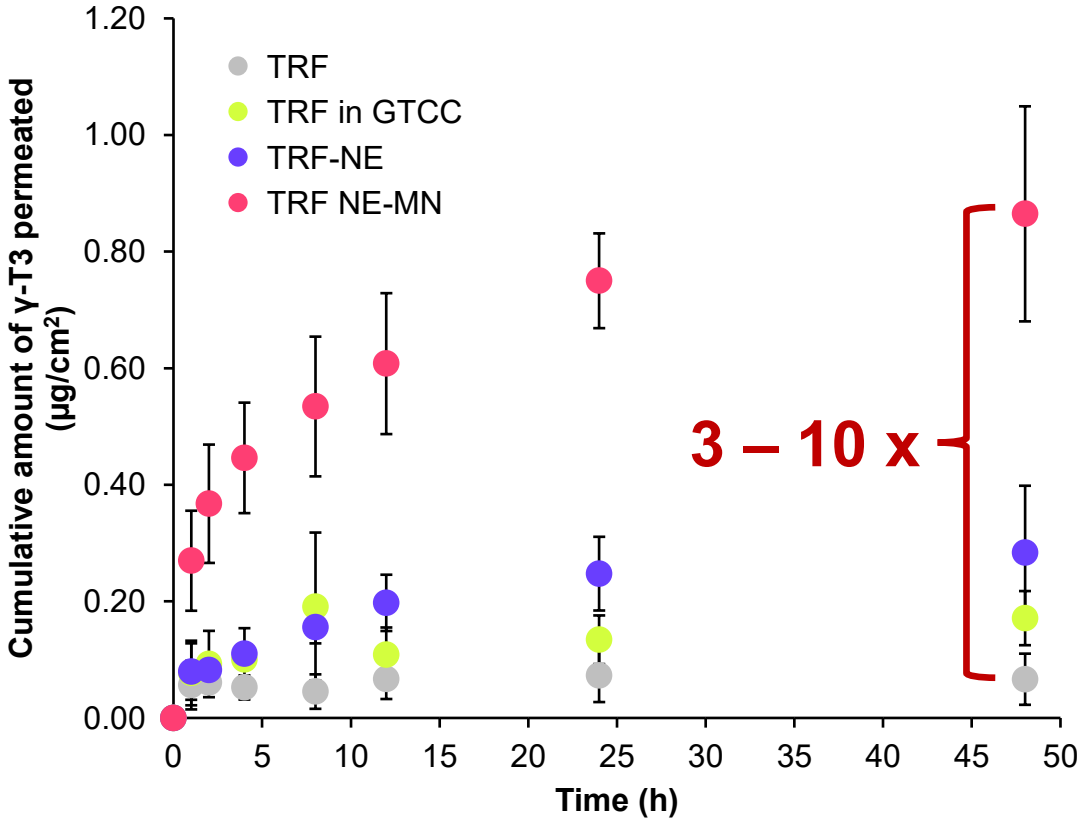
* Porcine ear skin was used

In vitro permeation and mass balance studies* of TRF NE-MN

TRF only:	**TRF in GTCC:**	**TRF-loaded NE:**	**TRF NE-MN:**
Infinite	Infinite (10%w/v TRF)	Infinite (8%w/v TRF)	Infinite (8%w/v TRF)
Dose: ~15 mg/cm^2	Dose: ~2 mg/cm^2	Dose: ~1.5 mg/cm^2	Dose: ~15 µg/cm^2

1/100x dose loaded

In vitro permeation studies



Mass balance studies

Solvents	Permeation		On skin (%)	In skin (%)	Total percentage (%)
	µg/cm^2	%			
TRF	0.07 ± 0.05	0.01 ± 0.01	74.28 ± 10.82	0.19 ± 0.07	74.47 ± 10.85
TRF in GTCC	0.172 ± 0.047	0.0074 ± 0.01	87.08 ± 6.99	0.02 ± 0.01	87.11 ± 6.98
NE	0.29 ± 0.12	0.02 ± 0.01	66.23 ± 14.52	1.12 ± 1.43	67.37 ± 13.13
TRF NE-MN	0.87 ± 0.19	5.6 ± 1.47	83.84 ± 20.3	3.49 ± 3.48	92.92 ± 22.95

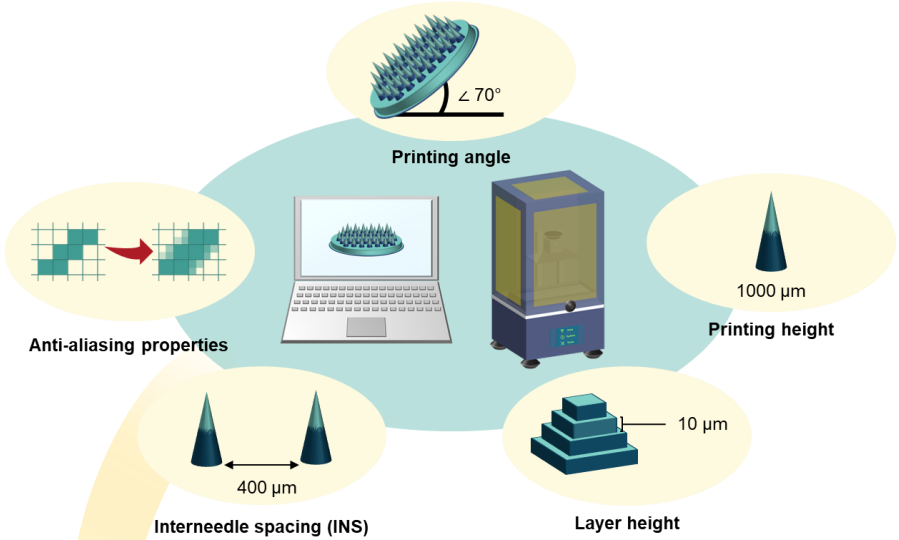
* Porcine ear skin was used

Conclusion

High lipophilicity of TRF
Amount permeated: < 0.07 μg/cm^2

Solvent

TRF in solvents
Amount permeated: ~0.15 μg/cm^2



Optimised and validated 3DP MN

TRF-nanoemulsion
Droplet size: < 200 nm
Amount permeated: ~0.3 μg/cm^2

TRF NE-MN
Amount permeated: ~1 μg/cm^2

Acknowledgements

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