Dissolving Microarray Patches for Malaria Chemoprophylaxis:

Mapping solid drug nanoparticle incorporation and long-acting release in vivo.

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CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
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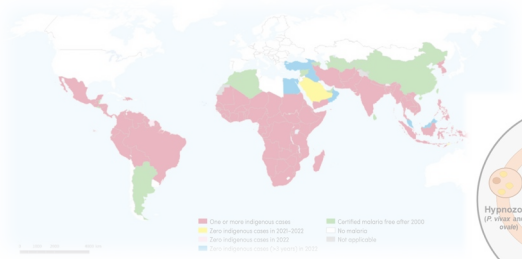
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

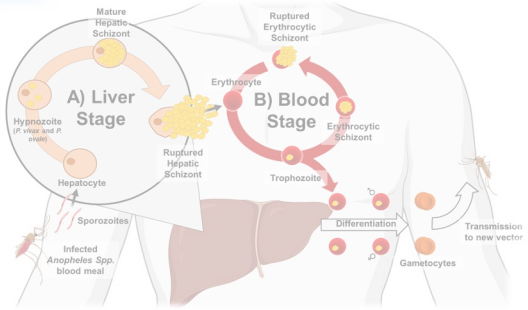
The Malaria Burden

Parasitic infection caused by *Plasmodium* spp. - exclusively transmitted by female *Anopheles* spp. mosquitos.

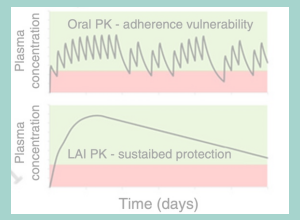
Yearly Statistics (2022):[1]

- **249,000,000** new infections.
- **608,000** deaths.
- **76%** of deaths occur in children under five years old.
- **Every second**, a child in Africa dies from malaria.





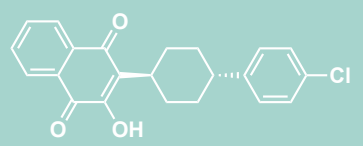
Previous work: Long-acting **injectable** formulation of atovaquone solid drug nanoparticles.[2]



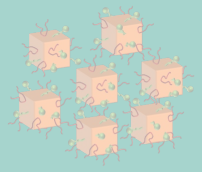
CELT

How might we improve adherence further?

Long-acting antimalarial patch based on combined nanoformulation and microneedle technologies.



Atovaquone



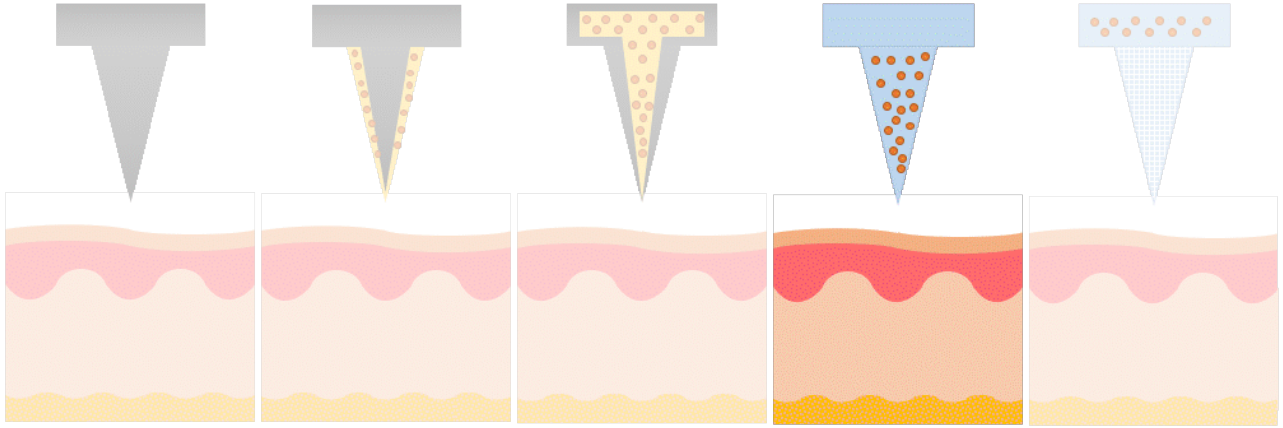
Solid drug nanoparticles

Loaded microarray patch

[1] World Health Organization, *World Malaria Report 2023*, 2023
[2] R.P. Bakshi *et al., Nat. Commun.*, 2018, **9**, 315

Microneedles

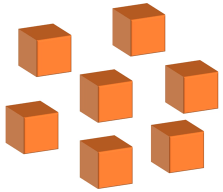
- Microneedles (MNs) as a Drug-Delivery System (DDS)
  - **Sub-millimetre** scale
  - Multiple MN architectures
  - **Enhance permeation** across a biological barrier (e.g. skin, cornea) while maintaining a **minimally-invasive** and **pain-free** profile.
- Dissolving Microneedles (DMNs)
  - Also known as dissolving microarray patches (DMAPs)
  - Pharmaceutical ingredient is incorporated within a water-soluble polymer matrix
  - Upon delivery, polymer dissolves to release the payload
  - Allows for circumvention of patient adherence issues such as **pill fatigue and needle phobia**
  - Suitable for deployment in **low-income areas**, dissolution removes the need for functional **sharps waste streams** associated with other MN technologies.



Images courtesy of:
E. Larraneta *et al., Pharm Res,* 2016, **33**, 1055-1073
J Chen *et al., Drug Dev. Ind. Pharm.*, 2013, **41**, 415-422
S. P. Davis *et al., IEEE Trans. Biomed. Eng.*, 2005, **52**, 909-15
S.P. Sullivan *et al., Nature Medicine*, 2010, **16**, 915-920
R. E. Lutton *et al., Int. J. Pharm.*, 2015, **494**, 417-429

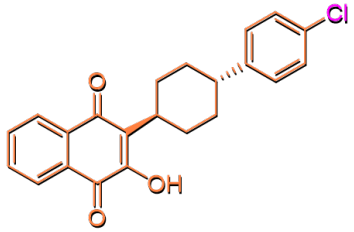
Formulation: Solid Drug Nanoparticles

Atovaquone (ATQ) exhibits very poor aqueous solubility (< 1 mg mL^{-1}). Its incorporation into a water-soluble DMAP therefore requires nanoformulation.



Aggregation

Milling to nanoscale

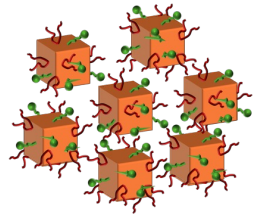


Atovaquone

Aq. Solubility < 0.2 µg mL^{-1}

Emulsion-templated

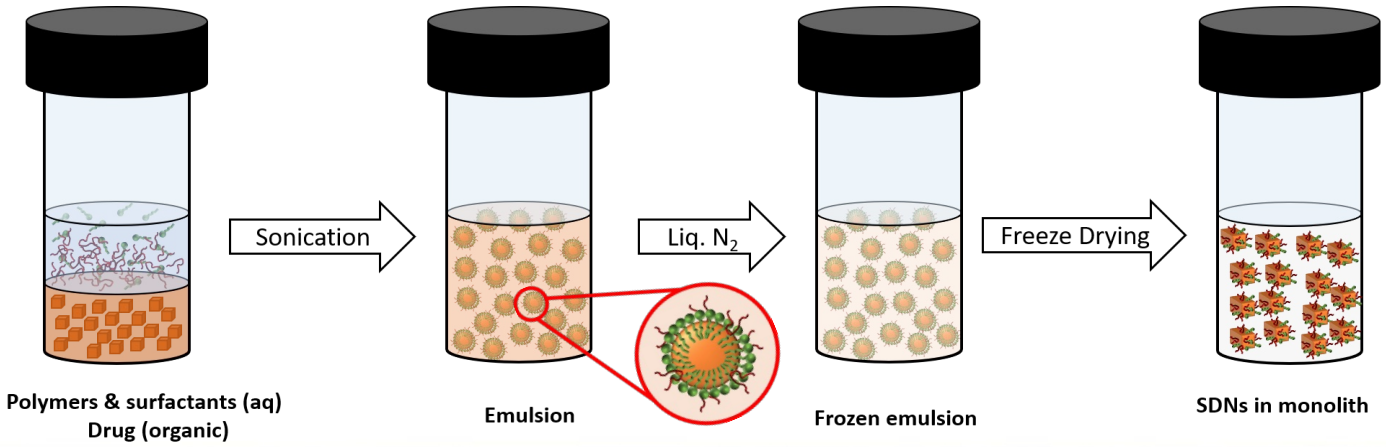
Freeze Drying (ETFD)



Solid Drug Nanoparticles
Water dispersible at ~400 mg mL^{-1}

Compatibility with polymeric DMAP substrates at very high [ATQ]

Nanoformulation approach: Emulsion-templated Freeze-drying (ETFD)

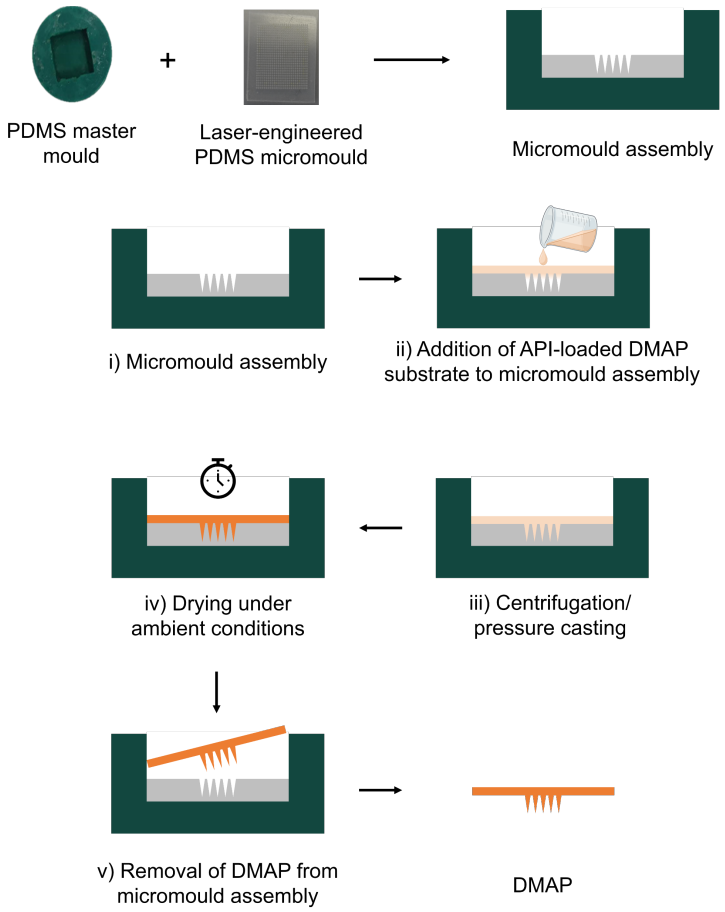


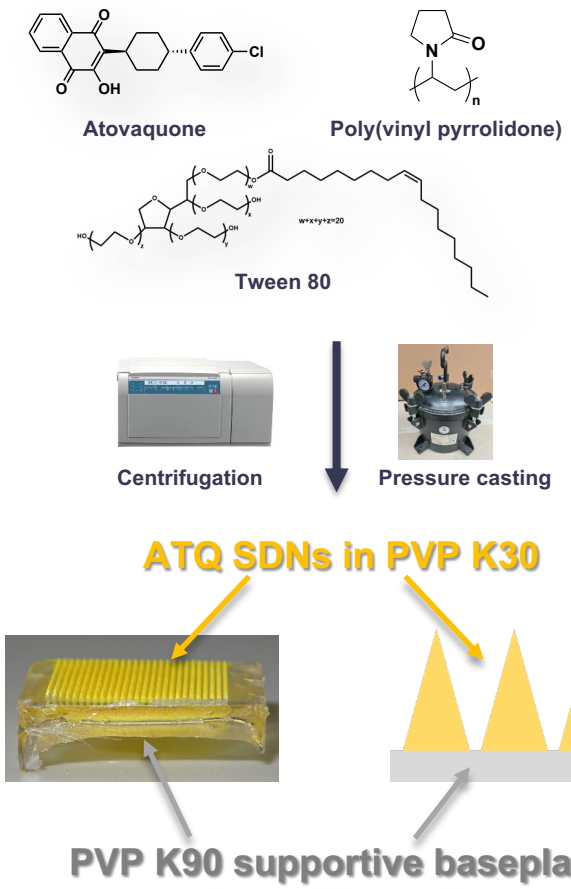
1) Generation of oil-in-water mixture of the drug (oil) and excipient stabilisers (water).
2) Energetic emulsification to form nanoscale oil droplets, stabilized by amphiphilic polymer and surfactant stabilisers (excipients).
3) Cryogenic freezing of the emulsion, trapping the stabilized oil droplets within a matrix of ice containing excess polymeric excipients.
4) Lyophilisation of the frozen emulsion. Solvents (water and organic) are removed leaving a porous polymer matrix with drug nanoparticles dispersed throughout.

Formulation: Dissolving Microarray Patches

ATQ SDN-loaded DMAPs formulated using a solvent casting micromoulding approach using a highly concentrated suspension of ATQ SDNs dispersed in a polymeric matrix. Poly(vinyl pyrrolidone) was used as the DMAP substrate.

Solvent casting micromoulding





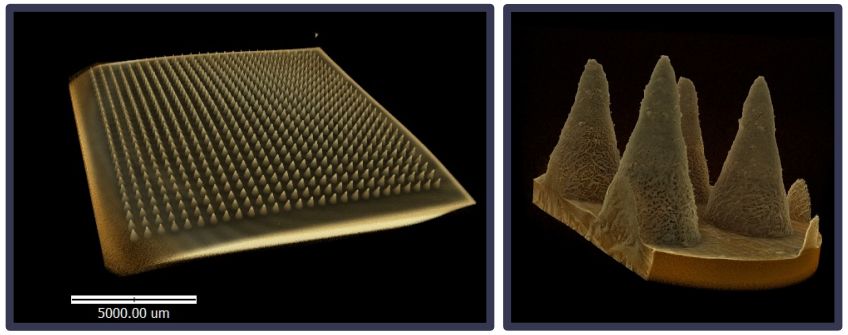


Fig. 1: 3D X-ray computerized microtomography reconstructions of ATQ SDN-loaded DMAPs. (Left) Overview reconstruction. (Right) High resolution offcut reconstruction.

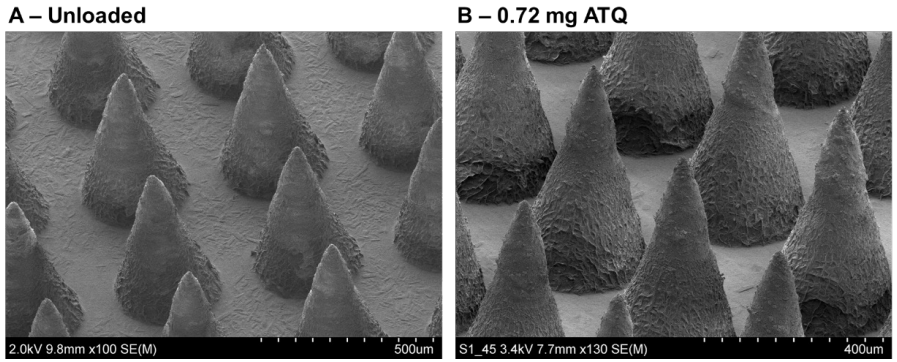
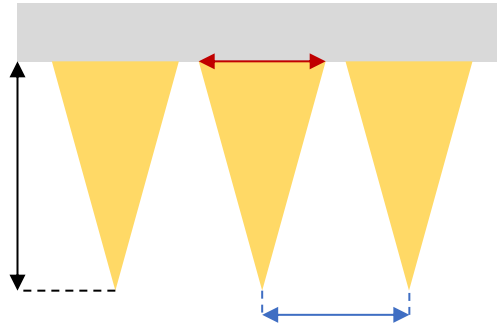


Fig. 2: Scanning electron micrographs of A) unloaded, PVP K30-based DMAP and B) DMAP loaded with 0.72 mg [ATQ] SDNs in PVP K30.

DMAPs – Important Characteristics

MN Dimensions

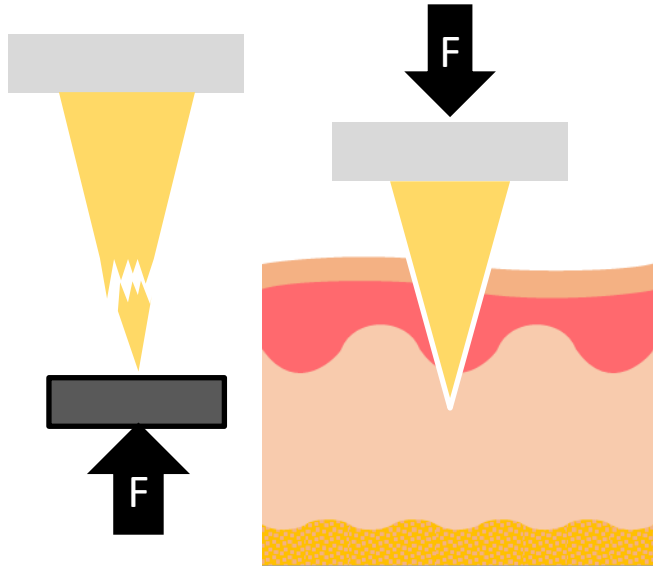


- MN height
  - Delivery of API to dermal microcirculatory system
- Base width
  - Insertion force *via* apex angle
- Interspacing
  - Insertion force *via* bed of nails effect

API Distribution

- Homogeneity of drug loading
- API concentration at microneedle tips preferable
- Possible effects of API distribution on mechanical properties?

Mechanical Properties



- MN integrity under compression
- Resistance to compression force
- Insertion force

DMAP Dimension Analysis

DMAP Dimensions should be controlled by the CAD design of the laser-etched micromould:

Microneedle (MN) height = 600 μm

Microneedle base width = 300 μm.

Microarray interspacing = 450 μm.

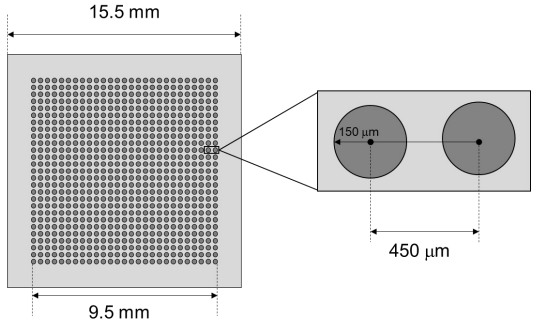


Fig. 1: CAD schematic of DMAP micromould.

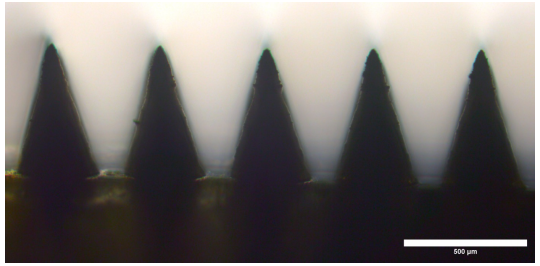
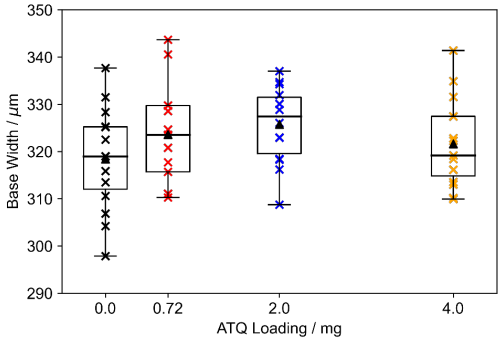
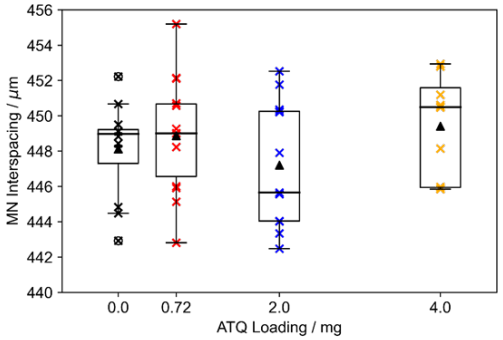


Fig. 2: Optical Microscope image of ATQ SDN-loaded DMAP.

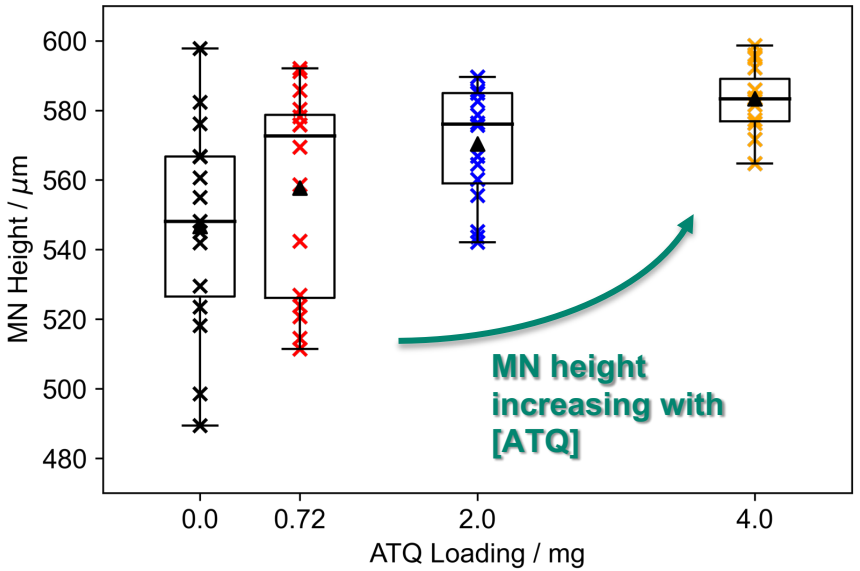
Base Width *via* Optical microscopy

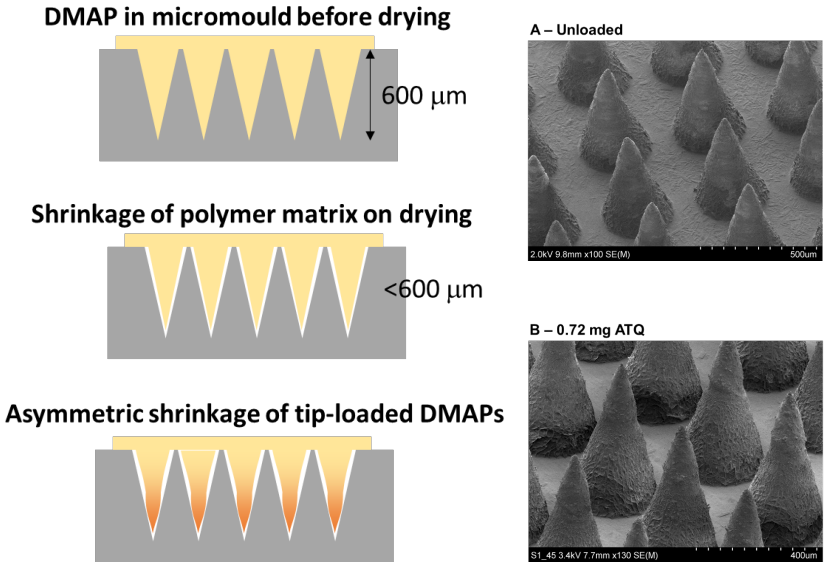


Interspacing *via* Optical Microscopy

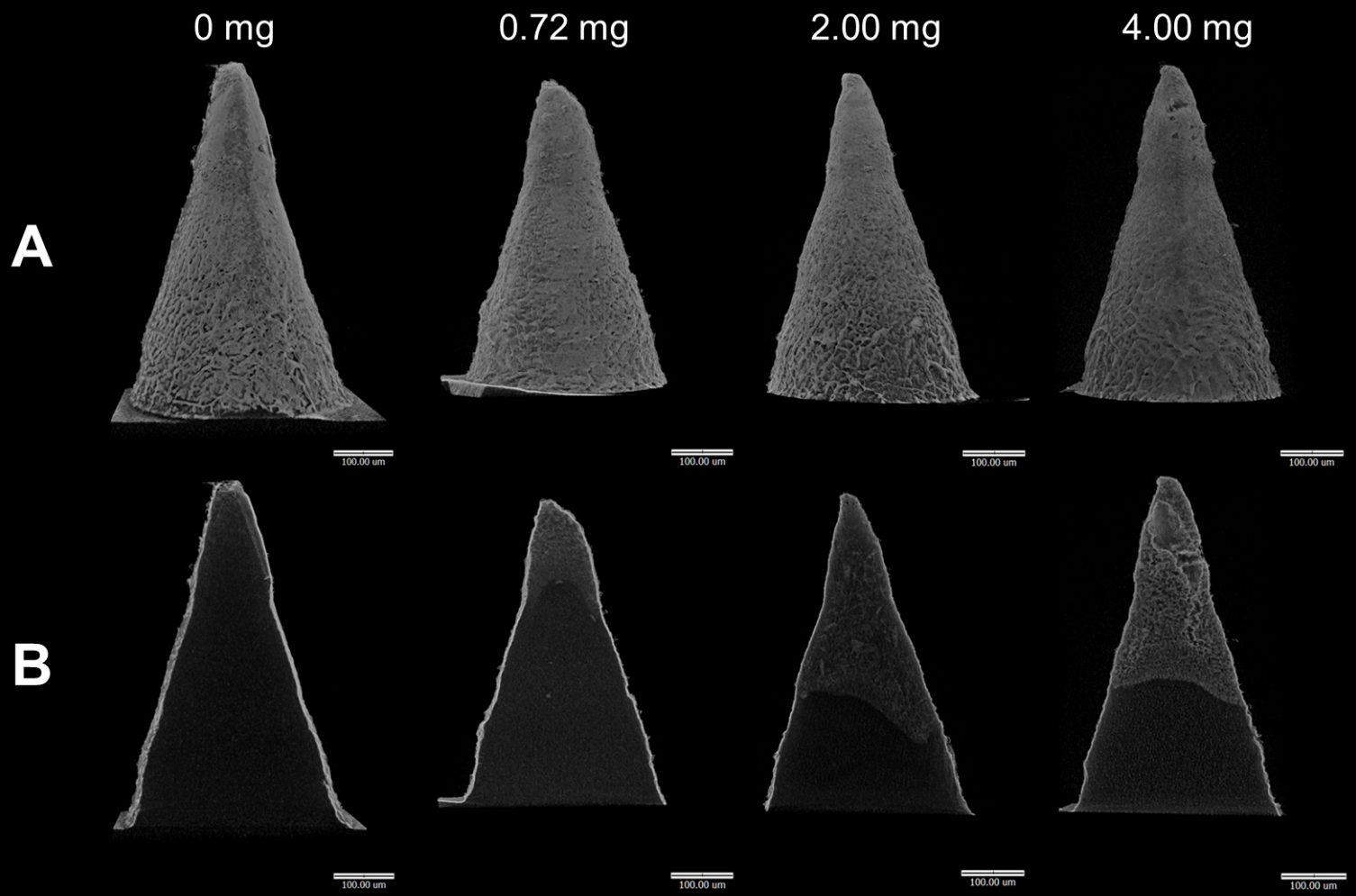


MN Height *via* Optical Microscopy

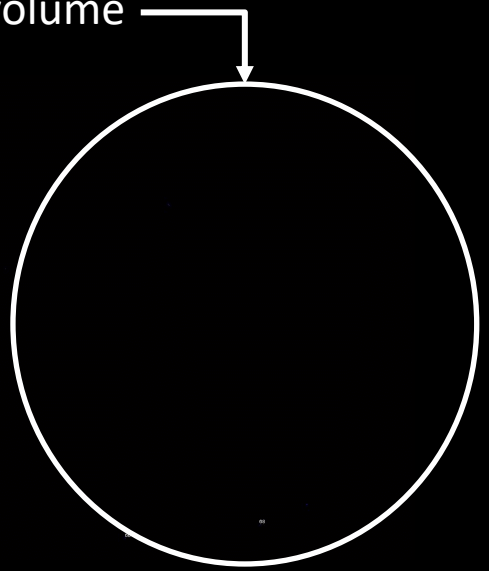




API Distribution – X-ray Computerised Microtomography (μCT)



- Contrast = density
- Increased density at MN tips implies ATQ tip distribution
- Voids in 4.00 mg DMAP – inefficient packing
  - Voids are *ca.* 8% of MN volume



Object map of 4.00 mg DMAP

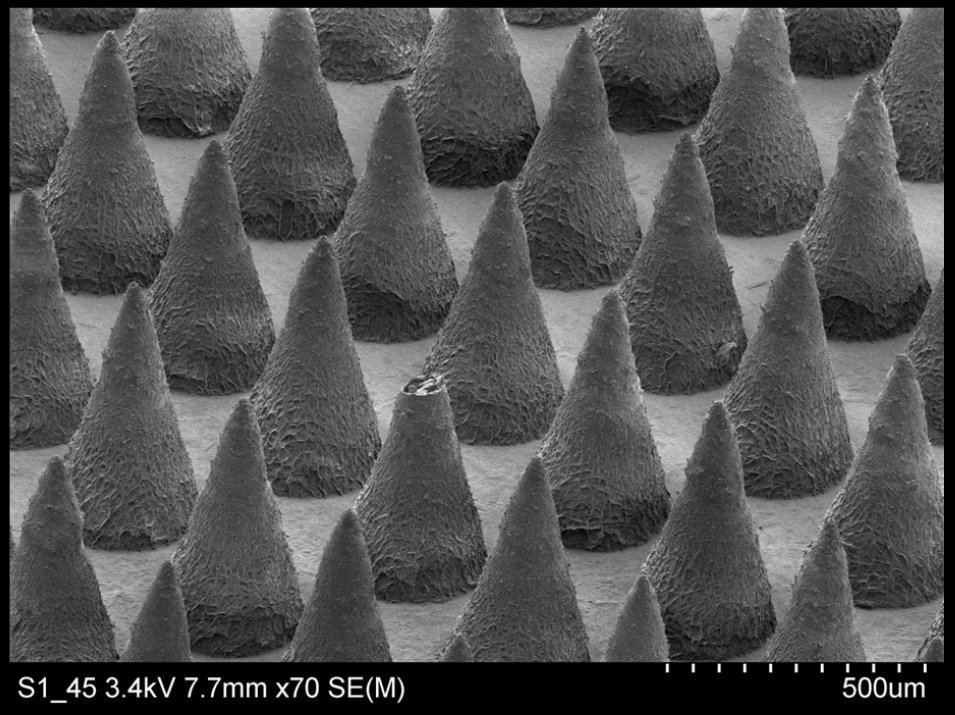
API Distribution – Scanning Electron Microscopy/Energy Dispersive X-ray spectroscopy

Scanning Electron Microscopy (SEM) revealed broken MN tip…

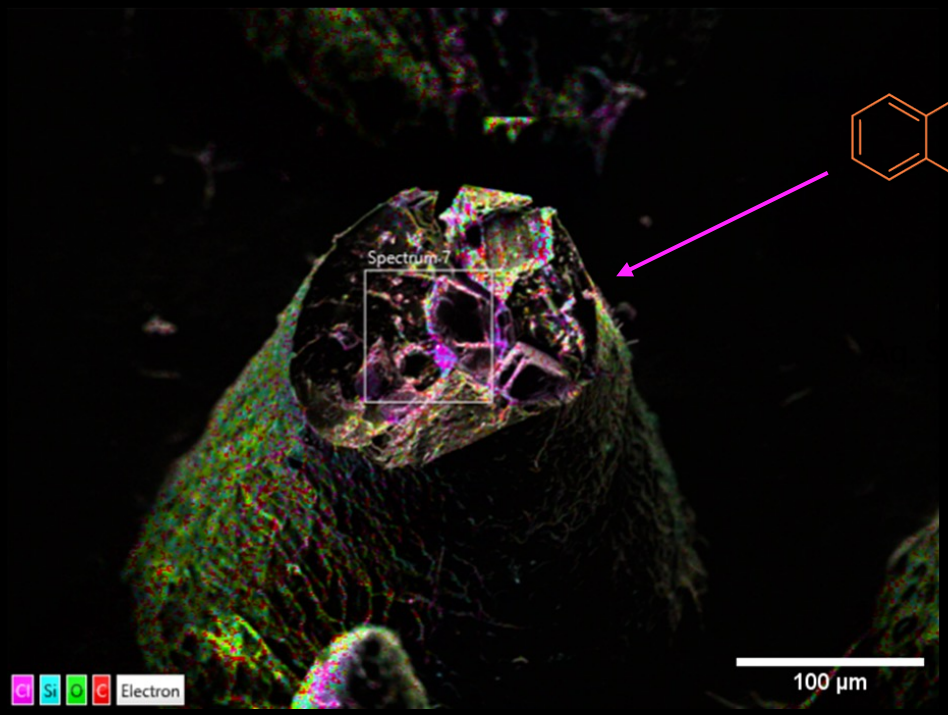
Energy-dispersive X-ray Spectroscopy (EDXS): Element mapping to SEM image

ATQ: $C_{22}H_{19}ClO_3$

A) SEM image of 0.72 mg ATQ DMAP (with broken tip)



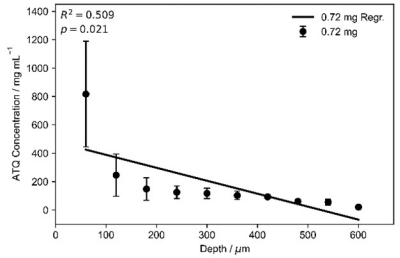
B) EDXS of broken tip



API Distribution – Radiometric Sectioning

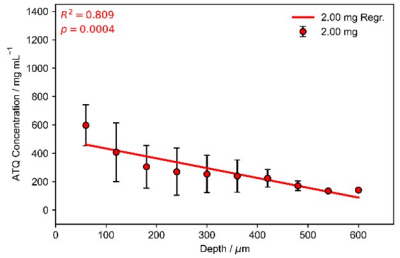
^{3}H-ATQ SDN-loaded DMAPs embedded in dental wax and sectioned *via* cryostat.

- Spatial ^{3}H-ATQ distribution profiles obtained *via* radiometric mass balance.



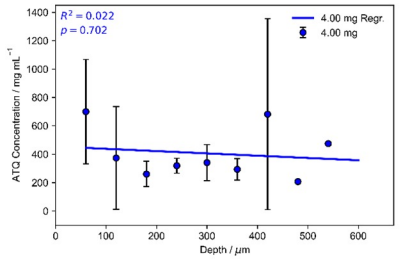
0.72 mg ATQ

- ATQ concentrated primarily in tip
- Gradual distribution thereafter



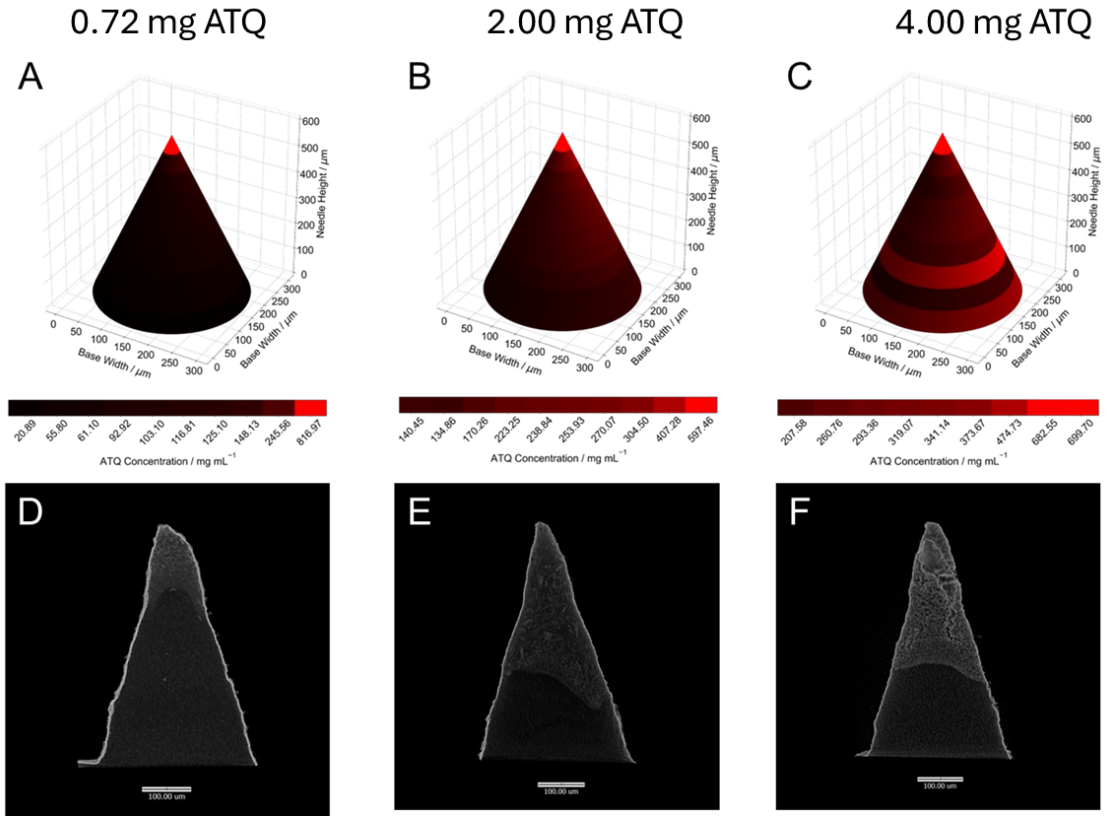
2.00 mg ATQ

- Less dramatic tip concentration
- More even distribution of ATQ across MNs



4.00 mg ATQ

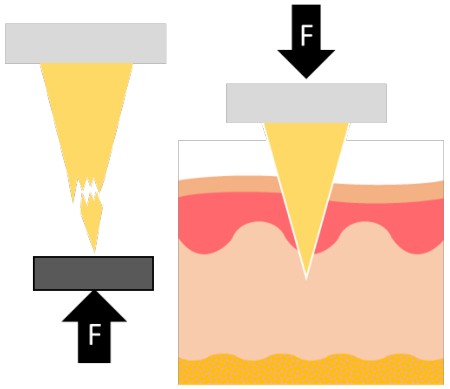
- Gradual distribution of ATQ
- Highest average ATQ concentration in tip
- Highly variable (voids?)



DMAP Mechanical Properties

$$\text{Young's Modulus } (E) = \frac{\sigma\ (force\ per\ unit\ area)}{\varepsilon\ (proportional\ deformation\ of\ sample)}\ ;\ Needle\ Modulus = \frac{Force\ applied\ per\ needle\ (N)}{\varepsilon}$$

Mechanical Properties

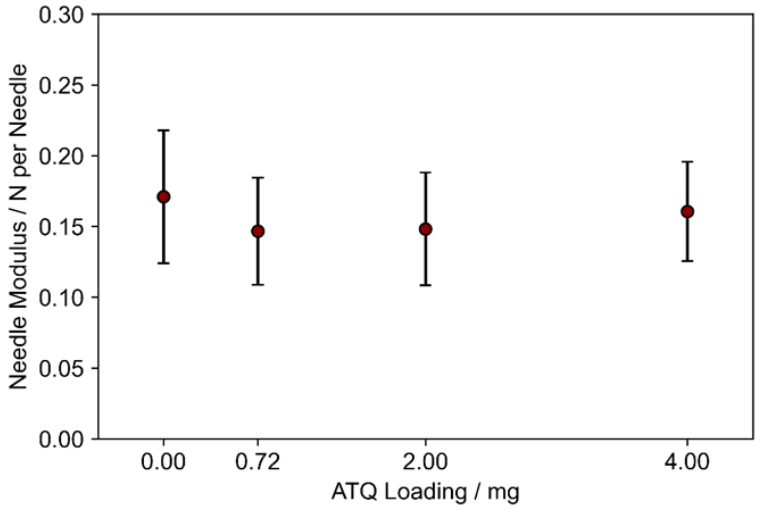


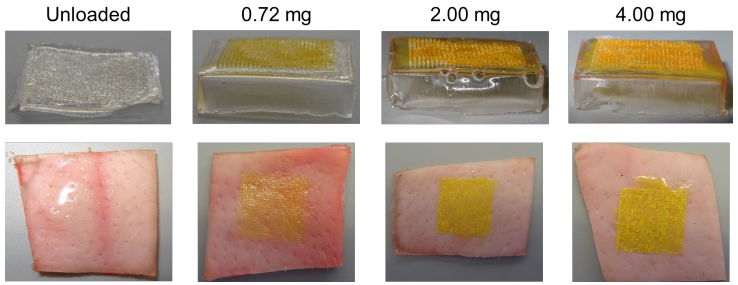
Resistance to axial compression did not vary with ATQ loading.

Complete DMAP insertion into *ex vivo* porcine skin attainable by patient-generable forces

- MN integrity under compression
- Resistance to compression force
- Insertion force

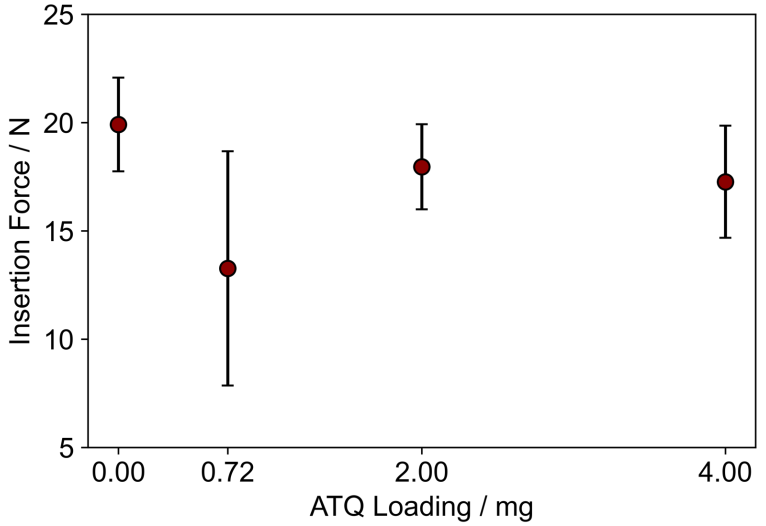
Needle moduli of ATQ SDN-loaded DMAPs





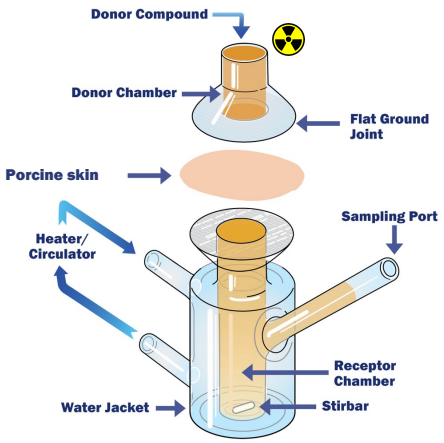
Dissolution and release of ATQ SDNs on ex vivo insertion

***Ex vivo* insertion force of ATQ SDN-loaded DMAPs**

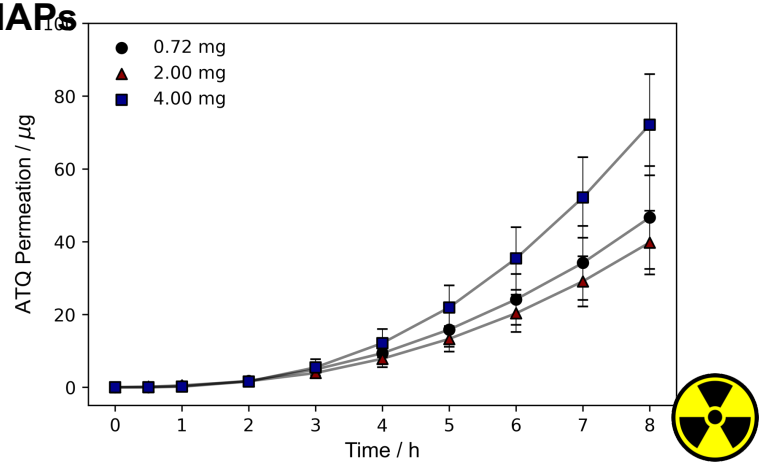


Ex vivo/in vivo Release

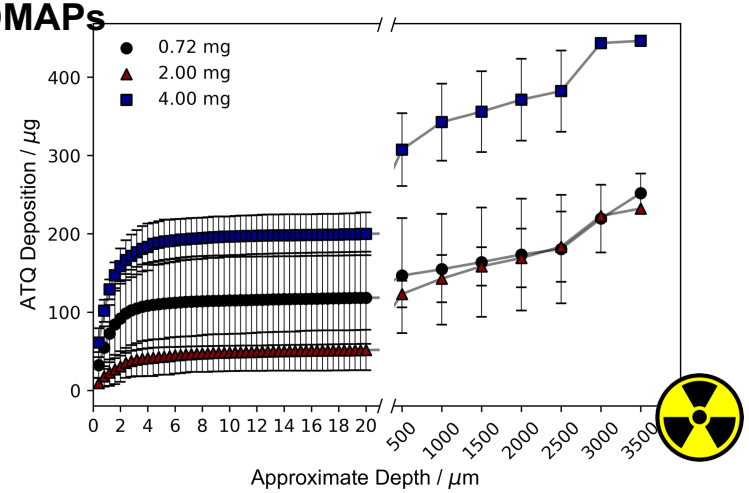
Ex vivo Radiometric Permeation/Deposition



Radiometric *ex vivo* permeation of ATQ from DMAPs

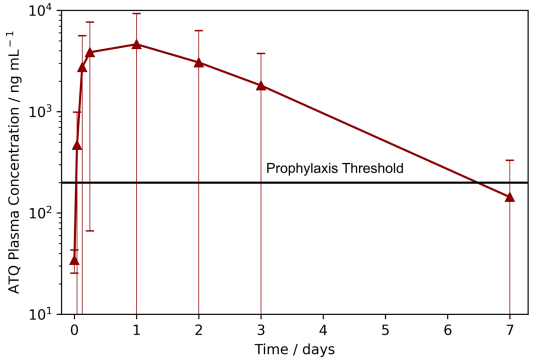


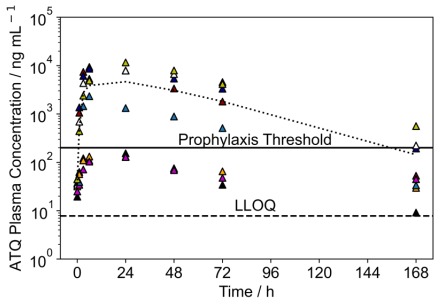
Radiometric *ex vivo* deposition of ATQ from DMAPs



In vivo Pharmacokinetics

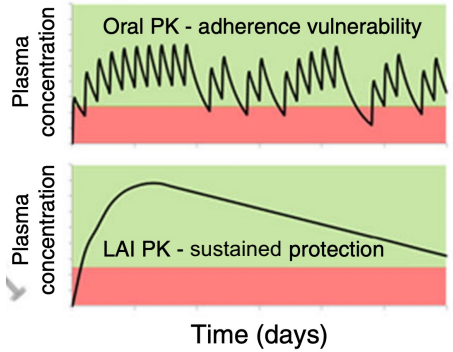
24-hour application of microarray patch...





**Response group deconvolution*

…up to 7 days of predicted prophylaxis following a single patch application.



Long-acting pharmacokinetics

Conclusions

- Successful formulation of highly concentrated ATQ SDN-loaded DMAPs
- ATQ is spatially concentrated towards MN tips within SDN-loaded DMAPs
  - DMAP morphology is affected but mechanical properties are not.
- Ex vivo permeation/deposition studies may indicate depot formation and sustained release.
- ATQ SDN-loaded DMAPs show long-acting release of therapeutically relevant concentrations of ATQ *in vivo* following a single patch application.

Acknowledgements

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Dr Usman Arshad
Dr Jo Sharp
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