Enhanced intradermal delivery of ivermectin using the combination of nanosuspensions and dissolving microneedles as a therapy for lymphatic filariasis

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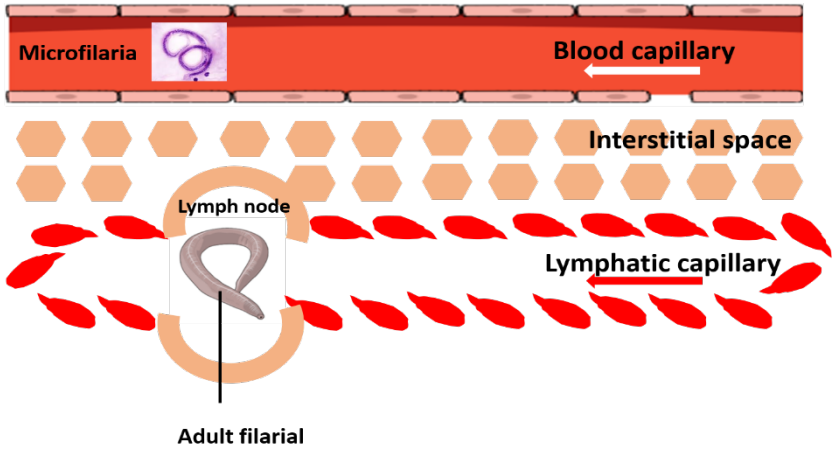
INTRODUCTION

LYMPHATIC FILARIASIS (LF)

Caused by

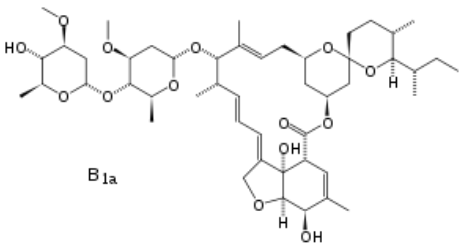
- *Wuchereria bancrofti*
- *Brugia timori*
- *Brugia malayi*



Neglected tropical disease in 52 countries

Affecting 886 million people worldwide

Oral administration of ivermectin (IVM)



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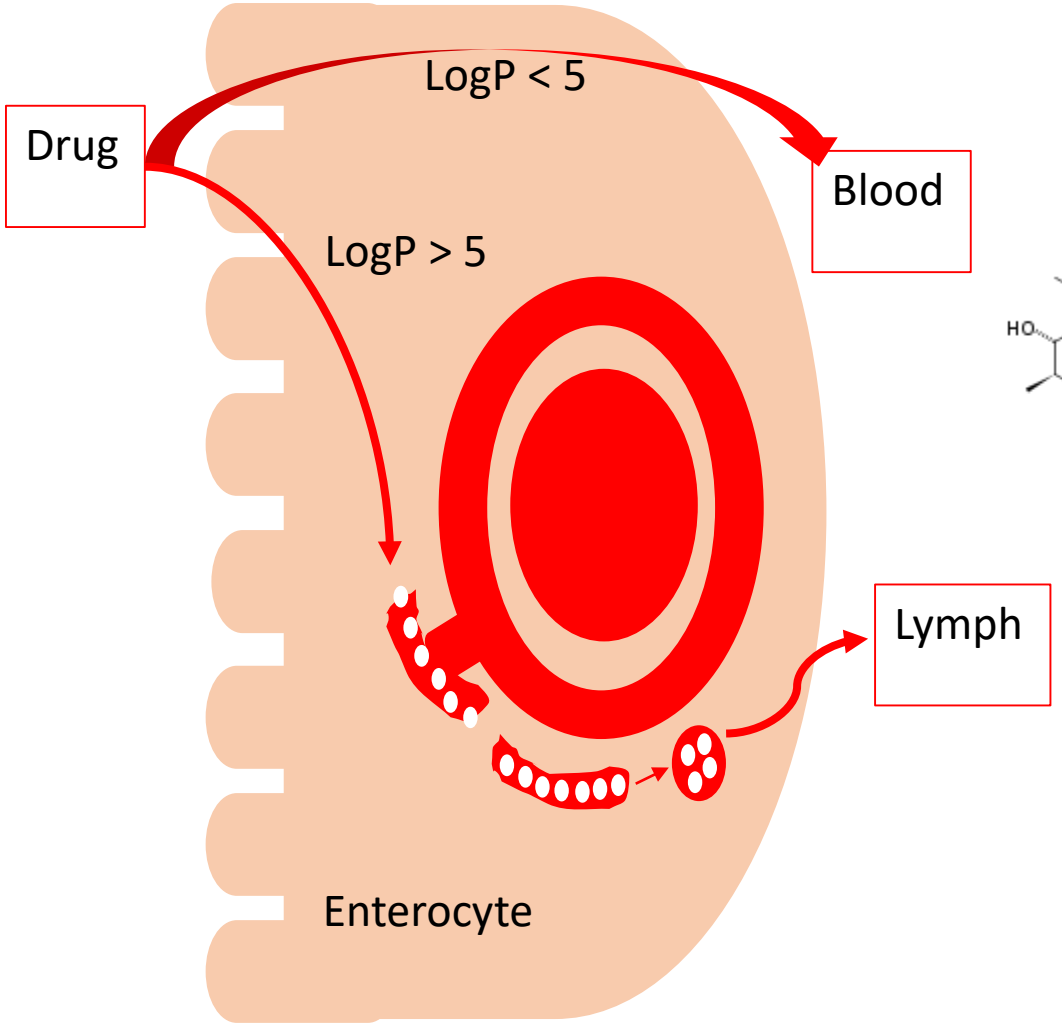
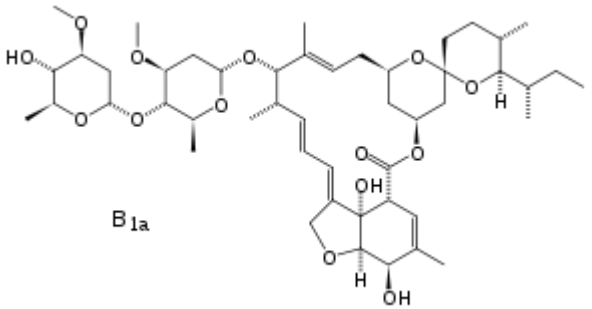


IVERMECTINE



LogP = 4.8

Effective to kill microfilariae in blood stream

Fail to kill adult filarial worms in lymph node

Ineffective therapy of LF

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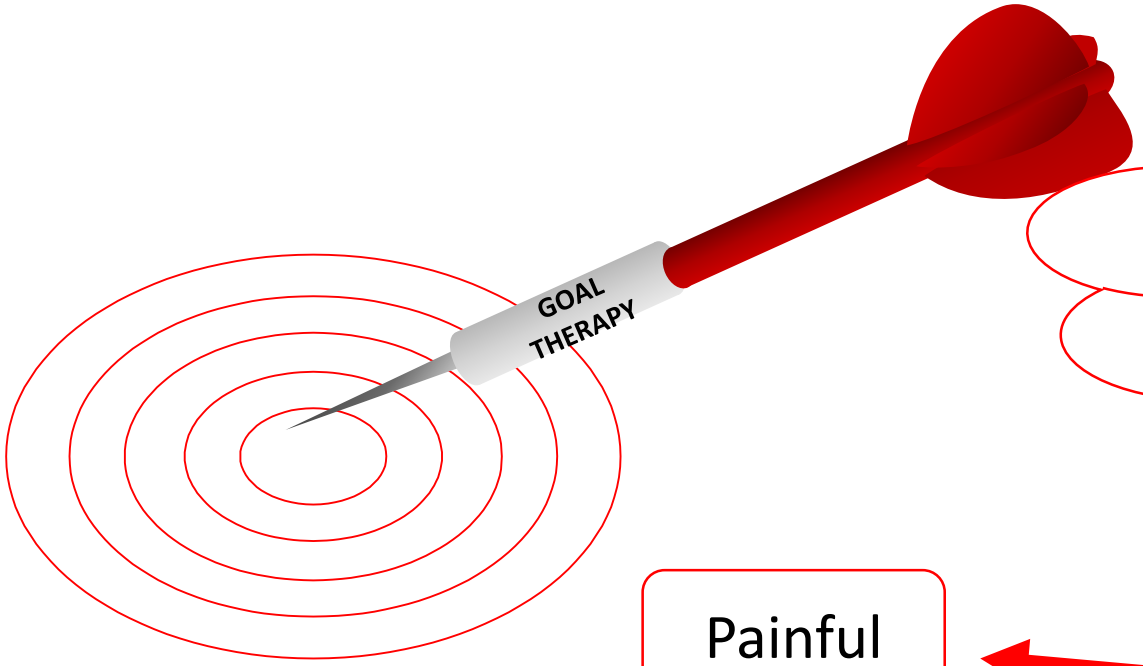

- Nanoparticle with sizes of 10-100 nm
- Intradermal delivery of nanoparticles

Intradermal injection

Painful

Unreliable

Less administration volume

Hazard clinical waste

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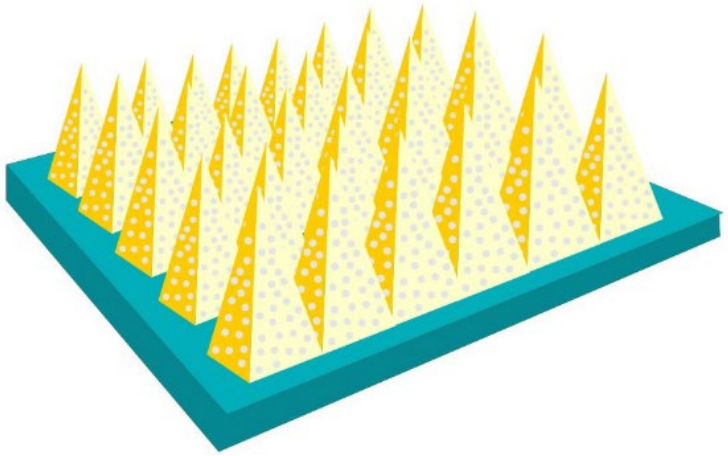
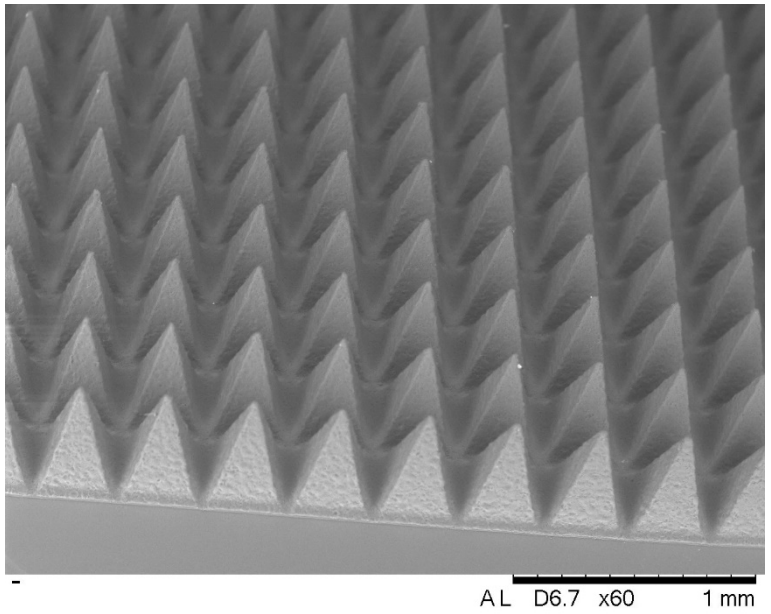
- Dissolving microneedles as innovative approach for intradermal delivery
- Painless
- Self-applicable
- No clinical waste
- More administration volume (larger patches)





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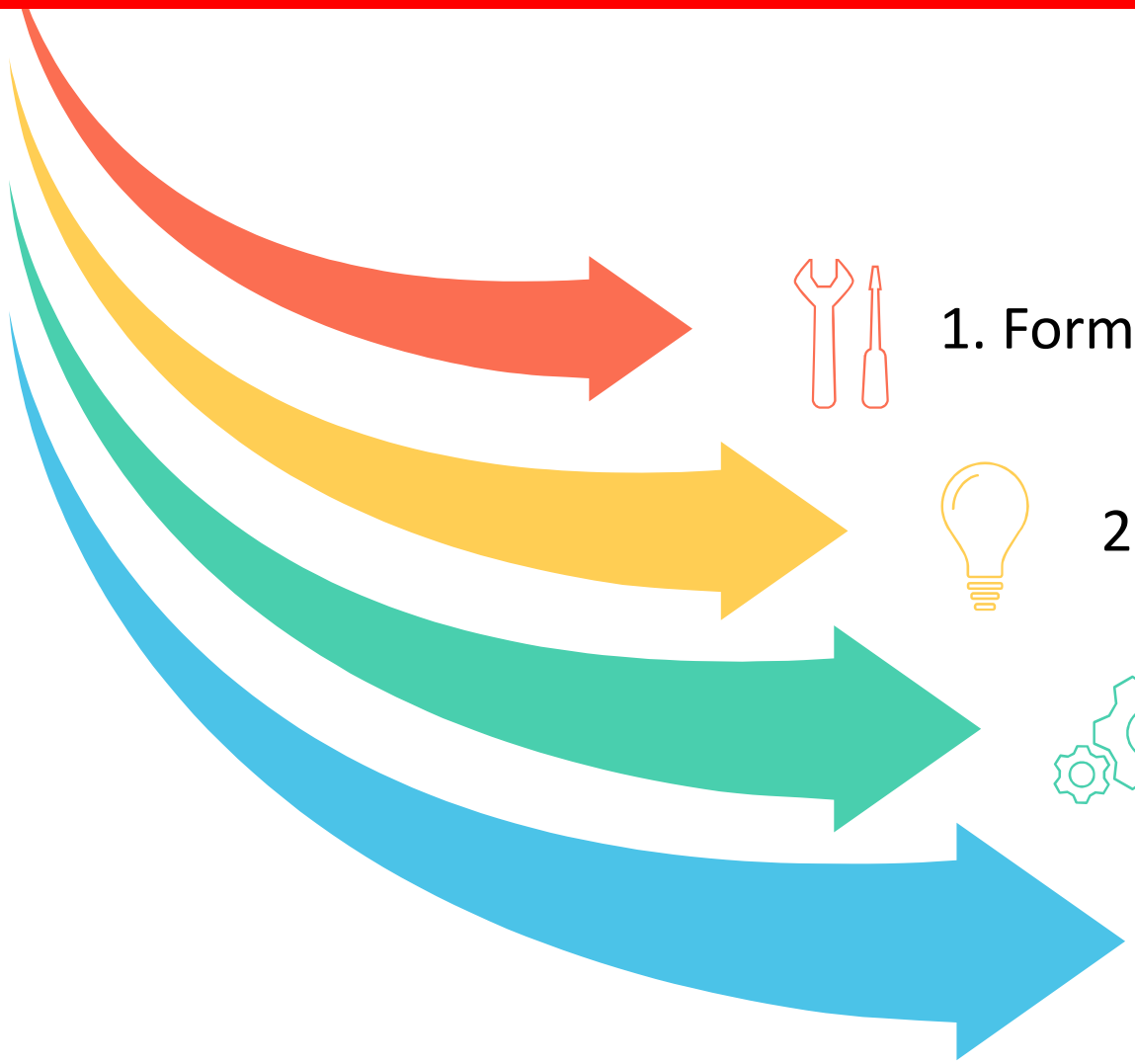
EXPERIMENTAL DESIGN



1. Formulation and optimisation of nanosuspension
2. Characterisation of nanosuspension
3. Formulation and characterisation of dissolving microneedle
4. Dermatokinetic and skin drug distribution studies

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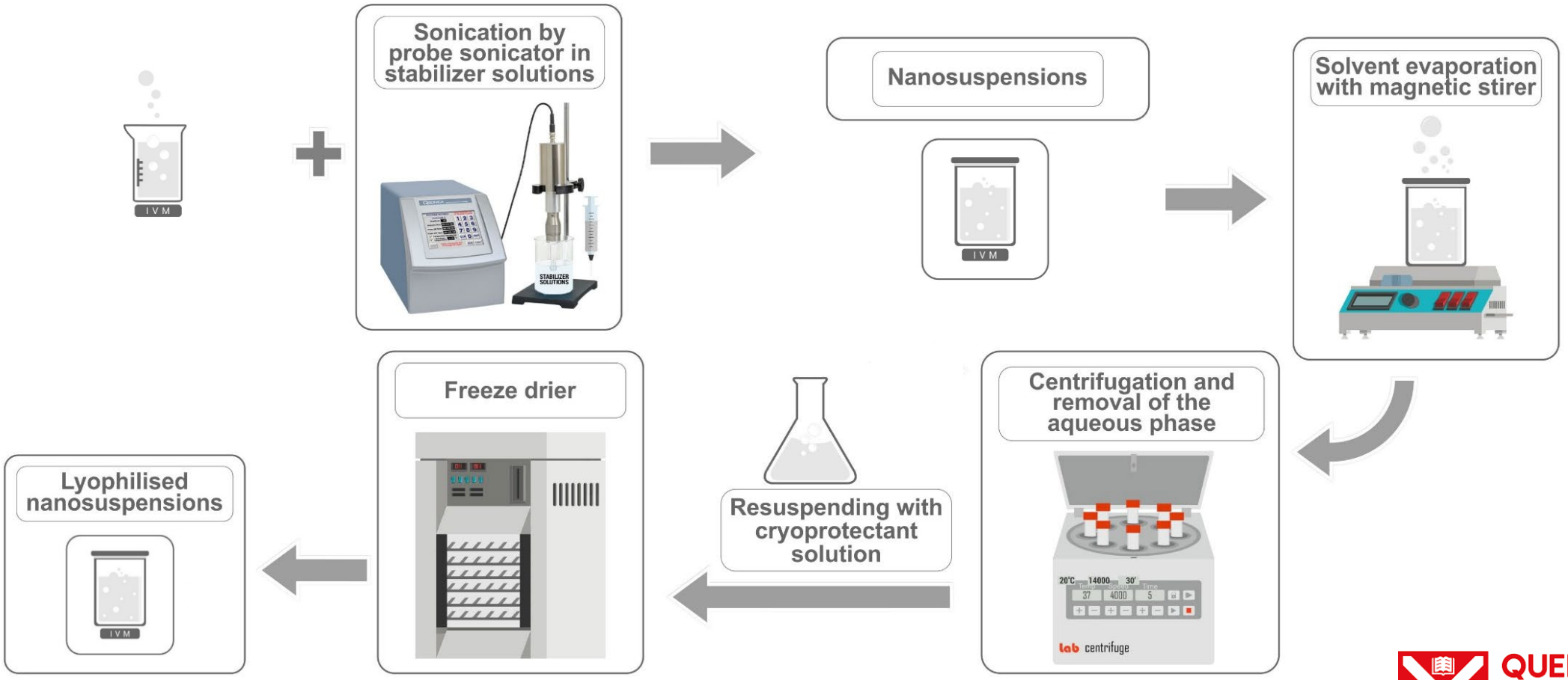
NANOSUSPENSION PREPARATION



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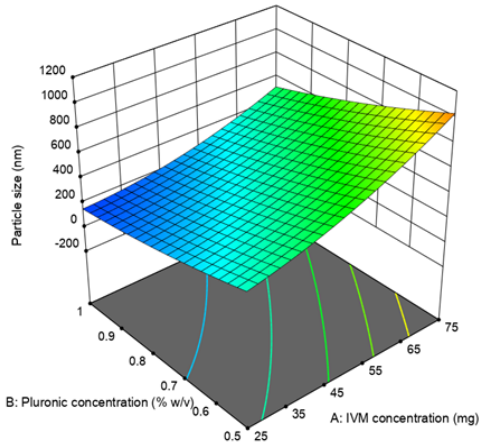
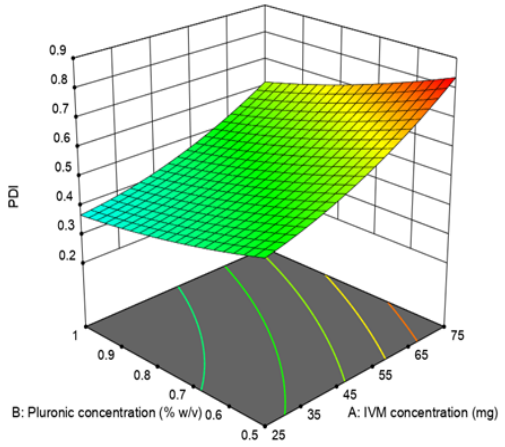
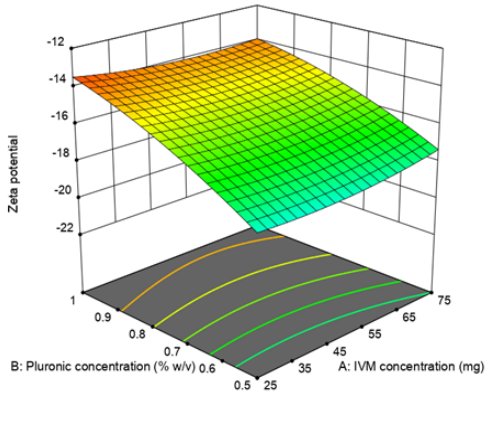
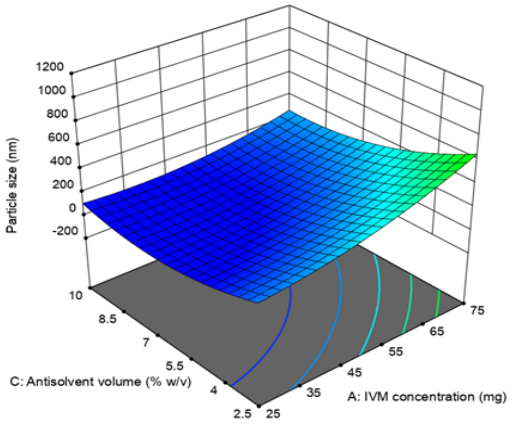
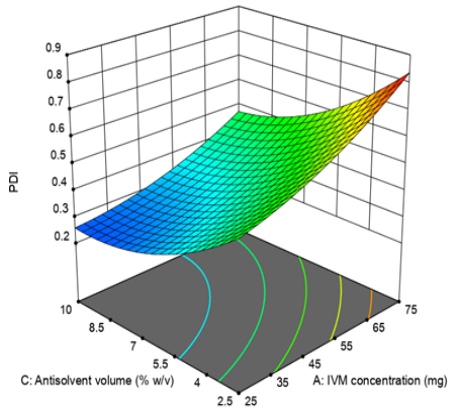
NANOSUSPENSION OPTIMISATION

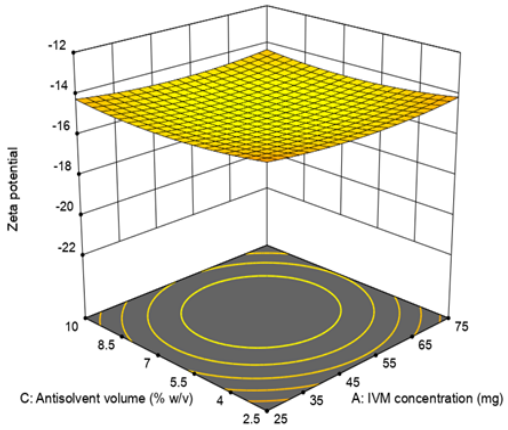












- Particle size: 98.12 ± 7.76 nm
- PDI: 0.233 ± 0.02
- Zeta potential: -15.07 ± 0.95

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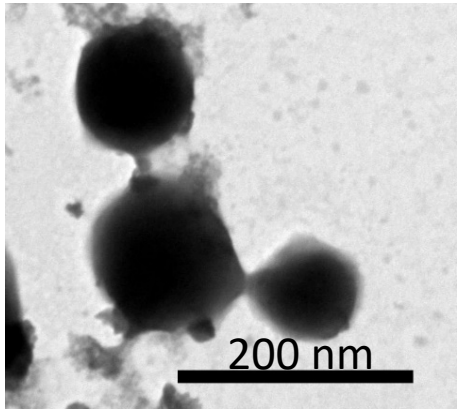
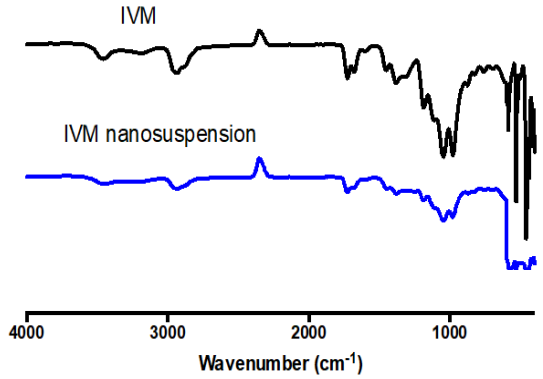
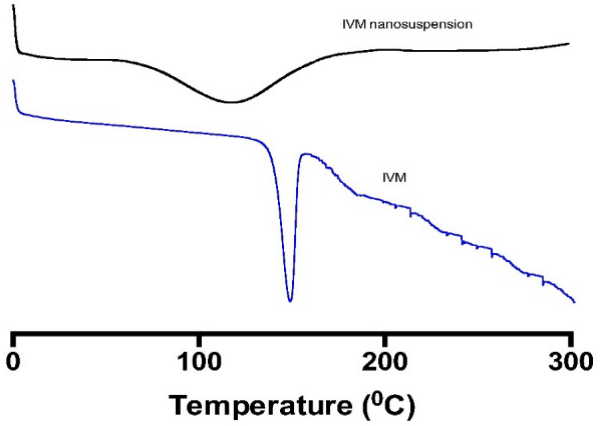
NANOSUSPENSION CHARACTERISATIONS



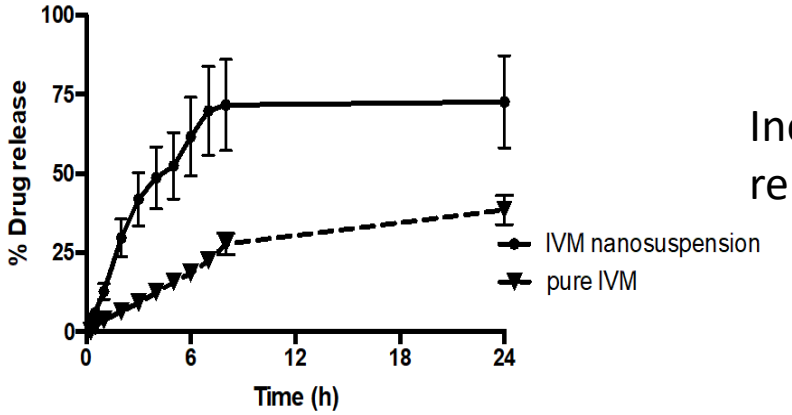
Spherical NS
(TEM)



No chemical interactions
(FTIR)



Changed from crystal
to amorphous
(DSC)



Increase cumulative
release after 24 h

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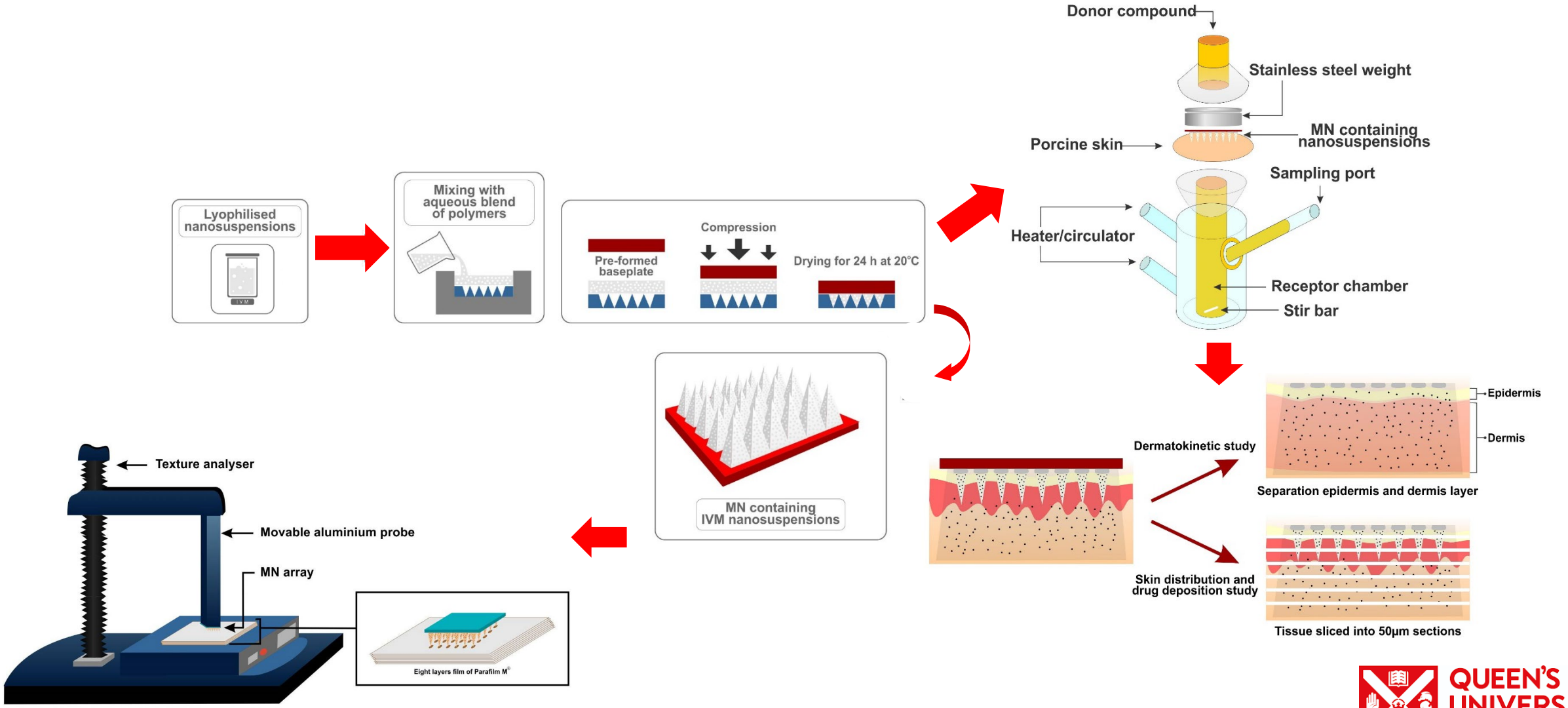
MICRONEEDLE PREPARATION



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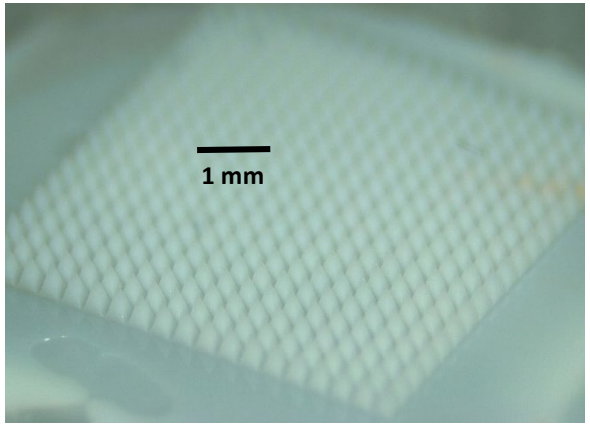
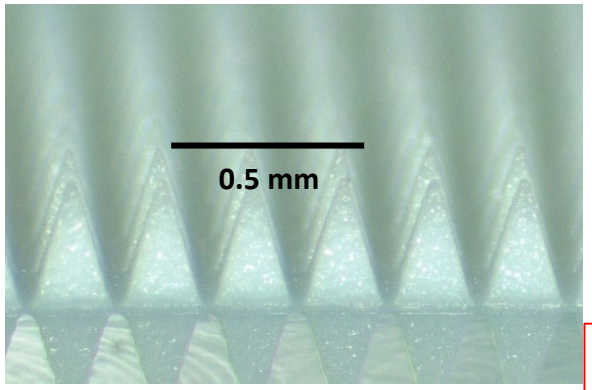
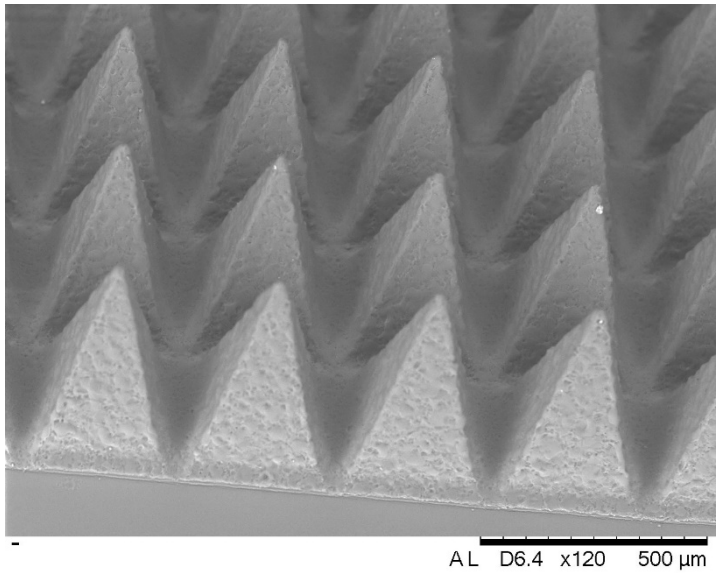
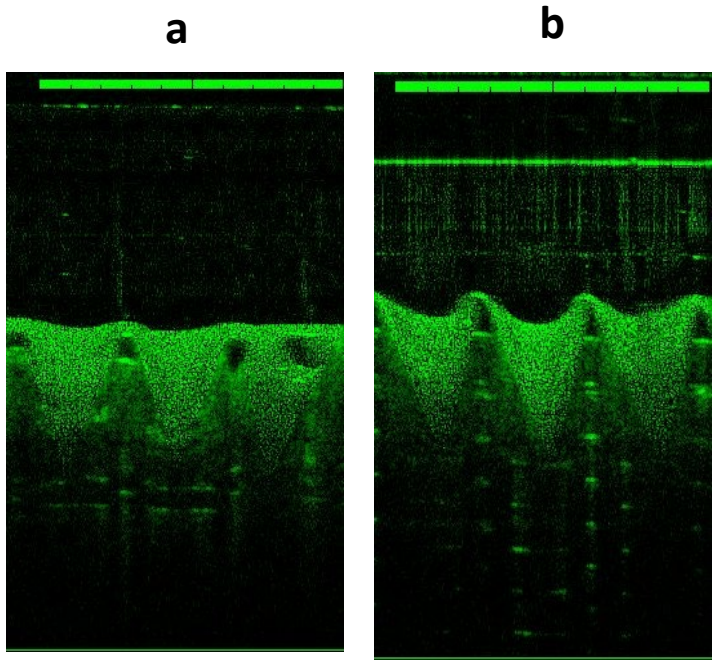
MICRONEEDLE CHARACTERISATIONS









Optical coherence tomography images in Parafilm®M (**a**)and porcine skin (**b**)

- MNs-NS exhibited homogenous MNs and had sharp tips
- 370.17 ± 17.13 µm of needles were inserted into Parafilm®M (skin stimulant)
- 369.22 ± 13.93 µm of needles were inserted into full-thickness porcine skin

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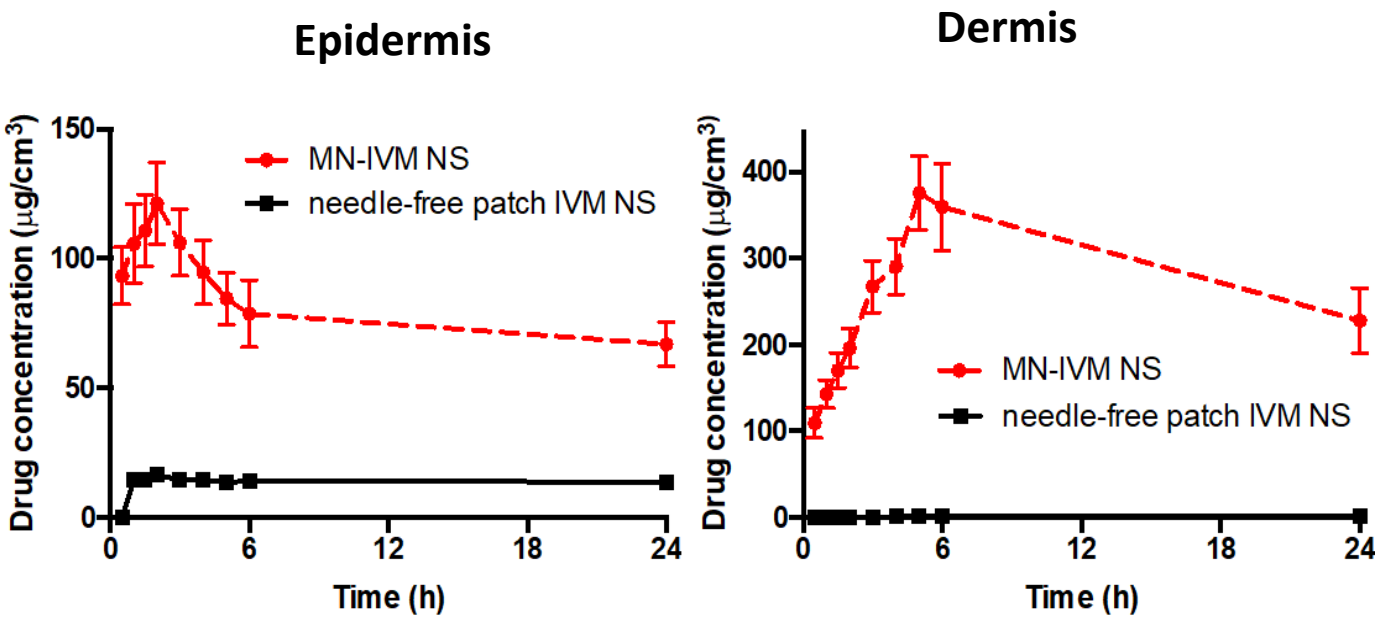
DERMATOKINETIC STUDY



- The values of C_{max} and AUC_{0-24} in the dermis was found to be significantly higher ($p < 0.05$) than in epidermis
- The values of C_{max} and AUC_{0-24} of drugs after MNs application were significantly higher ($p < 0.05$) than needle-free patch application in epidermis and dermis

	Dermatokinetic parameters (MNs)		
	AUC_{0-24} (μg/cm³/h)	t_{max} (h)	C_{max} (μg/cm²)
Epidermis	2018.92 ± 342.32	1.37 ± 0.29	108.02 ± 19.71
Dermis	7122.40 ± 784.09	8.01 ± 1.23	372.07 ± 49.98

	Dermatokinetic parameters (Needle-free patch)		
	AUC_{0-24} (μg/cm³/h)	t_{max} (h)	C_{max} (μg/cm³)
Epidermis	333.01 ± 73.21	4.35 ± 0.86	15.11 ± 3.05
Dermis	33.63 ± 6.83	11.51 ± 3.34	1.72 ± 0.55

- Considering the drug amount in the actual needles of the arrays, 34.54 ± 4.98% of IVM were retained in the dermis after 24 h administration.

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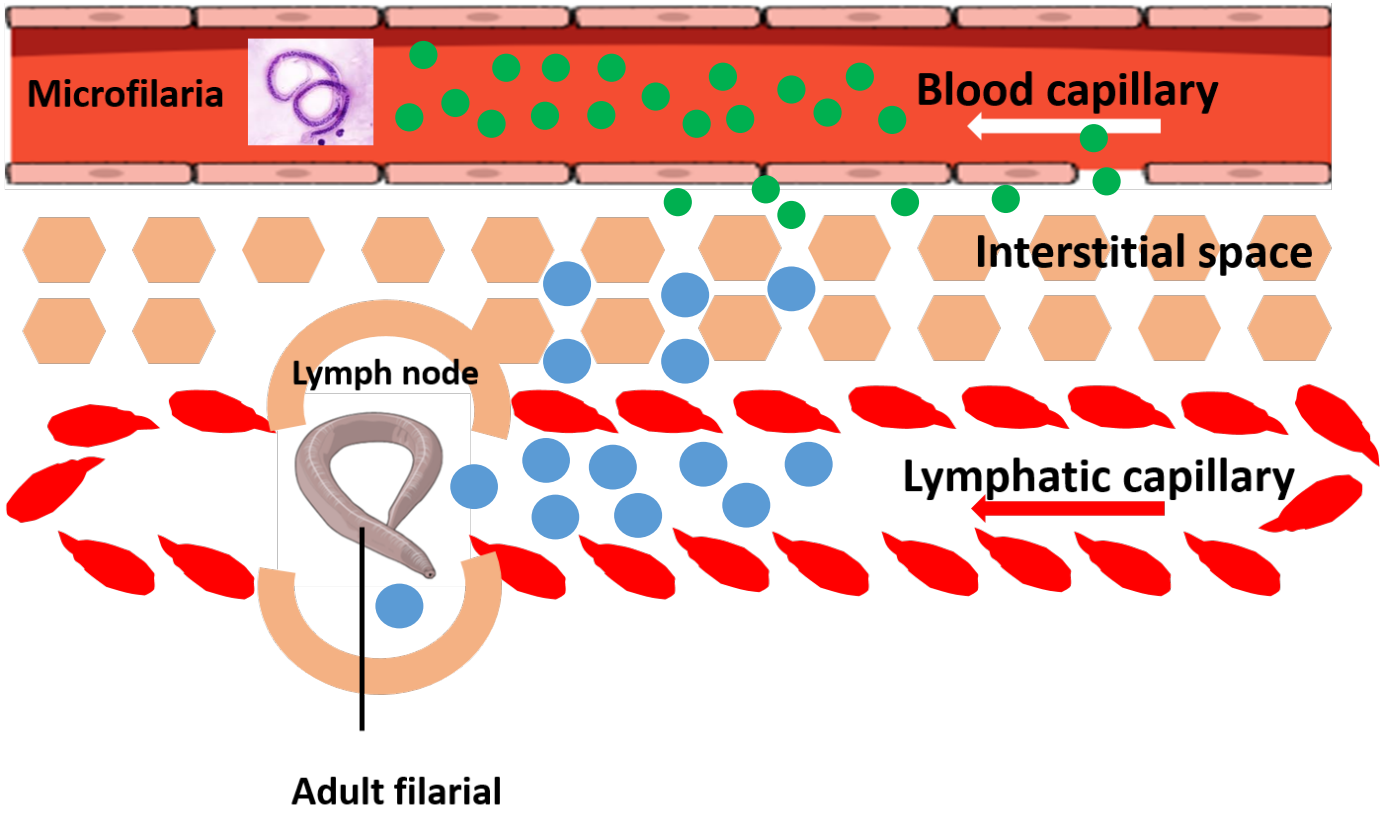
DISCUSSION



IVM Nanosuspension

Free IVM

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CONCLUSIONS

- Nanosuspension of IVM was successfully developed and optimised using central composite design to achieve the requirement of lymphatic uptake
- The incorporation of nanosuspension into MN arrays significantly improve the delivery of IVM into the dermis
- Further studies are required to determine the concentrations of drugs which reach the infection site *in vivo*

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pharmaceutics

MDPI

Article

Enhanced Intradermal Delivery of Nanosuspensions of Antifilariasis Drugs Using Dissolving Microneedles: A Proof of Concept Study

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