Novel Dissolving and Hydrogel-Forming Microarray Patches for Transdermal Delivery of Apomorphine HCl

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NEXT-GENERATION DELIVERY INNOVATIONS

Summary


Background

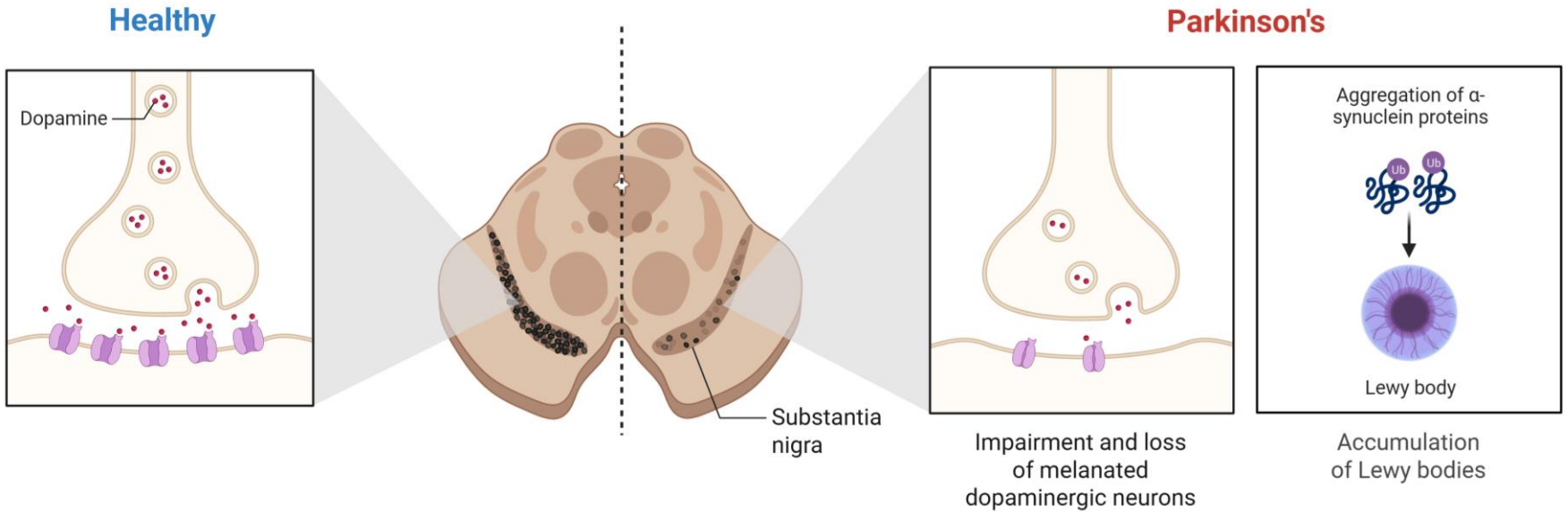

Project Aim


D-MAPs

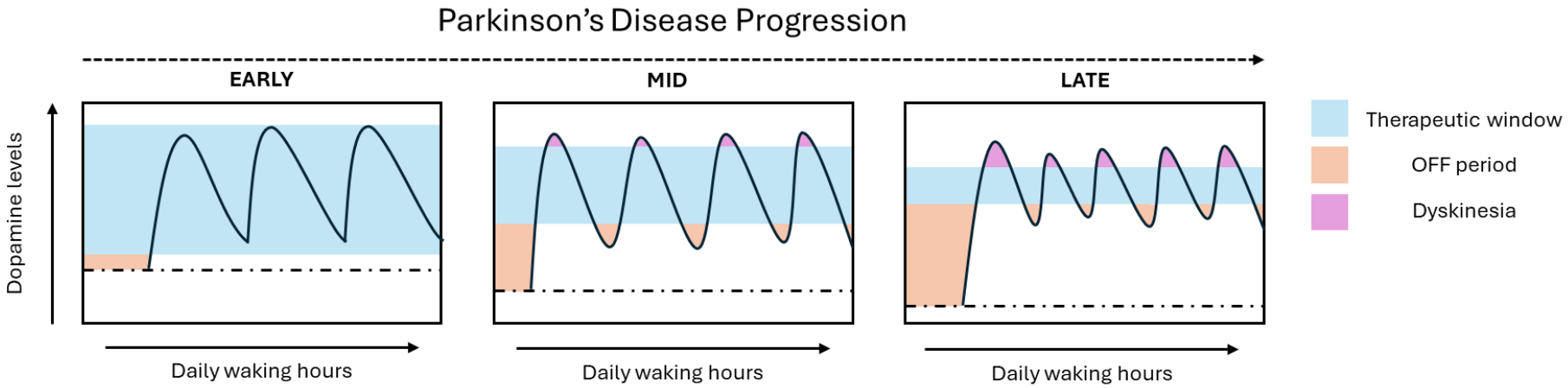

HF-MAPs


Conclusions and Future Outlook

Parkinson’s Disease



Dopamine Replacement Therapy (DRT) and OFF Periods



SYMPTOMS

- Tremor

- Stiffness or bradykinesia

- Nonmotor (Anxiety, depression)

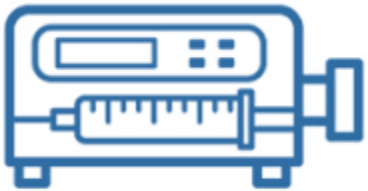
Challenges of Apomorphine (APO) DRT

SUBCUTANEOUS INJECTION

- *Difficult self-administration*
- *Pain / fear*
- *Intermittent*

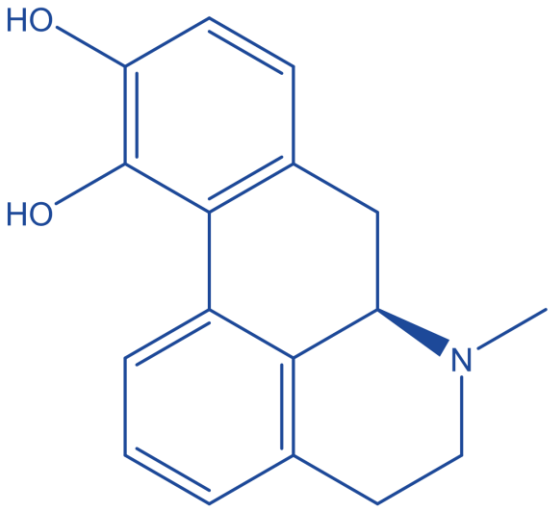
SUBLINGUAL FILM

- *Oropharyngeal side effects*
- *Poor uptake / high discontinuance*
- *Intermittent*



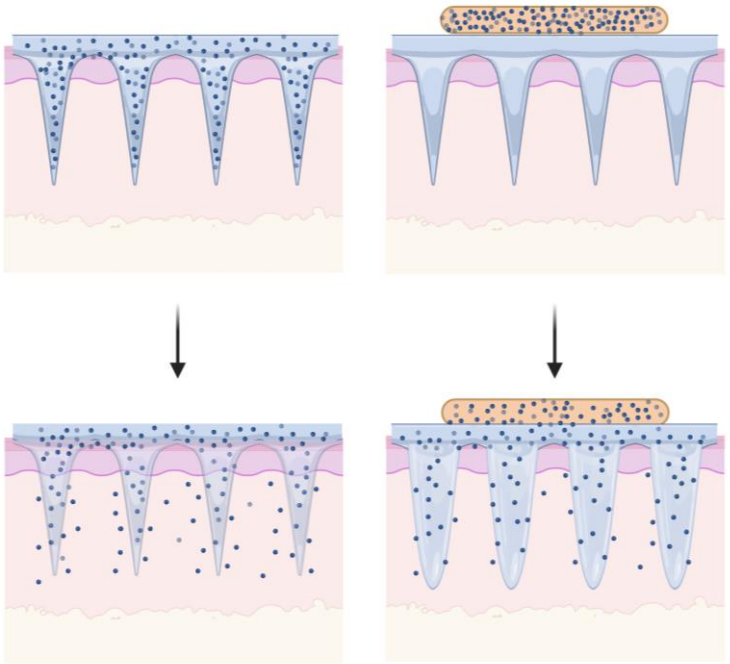
SYSTEMIC SC INFUSION

- *Complex self-assembly*
- *Pain / fear*



.HCl

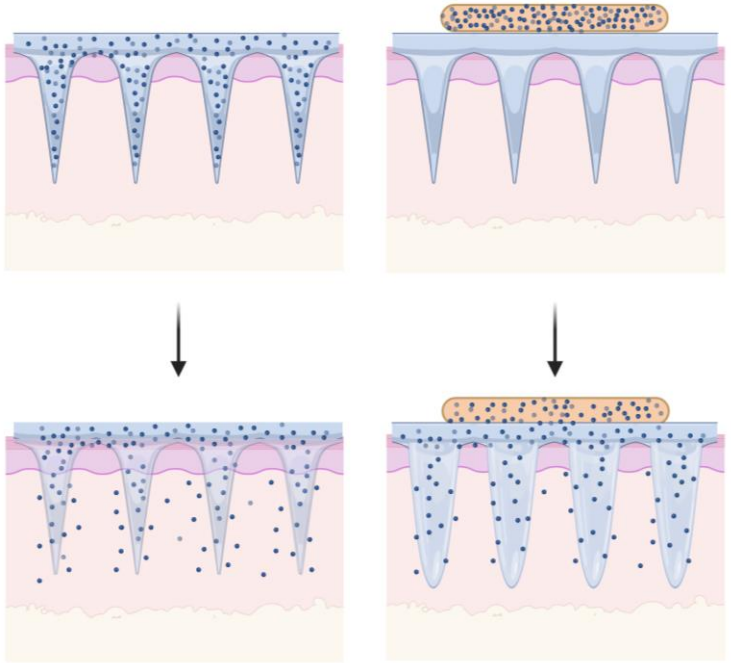
How can transdermal delivery *via* MAPs help?



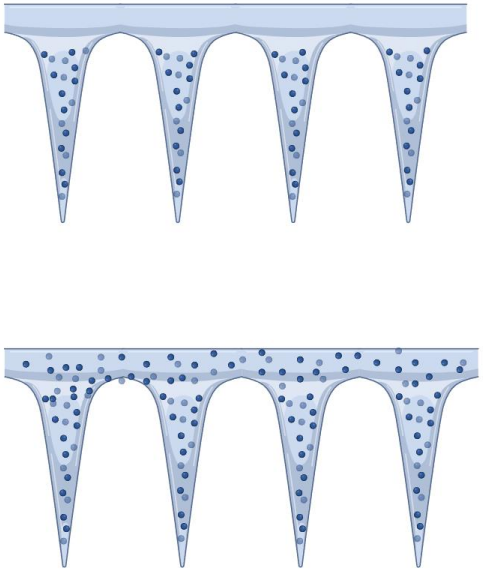
- Easy to self-administer
- Pain-free
- Minimally invasive
- Sustained release – reduced administration frequency
- Solid-state – improved stability

Project Aim

Design and characterise novel D-MAP and HF-MAP systems for sustained transdermal release of APO

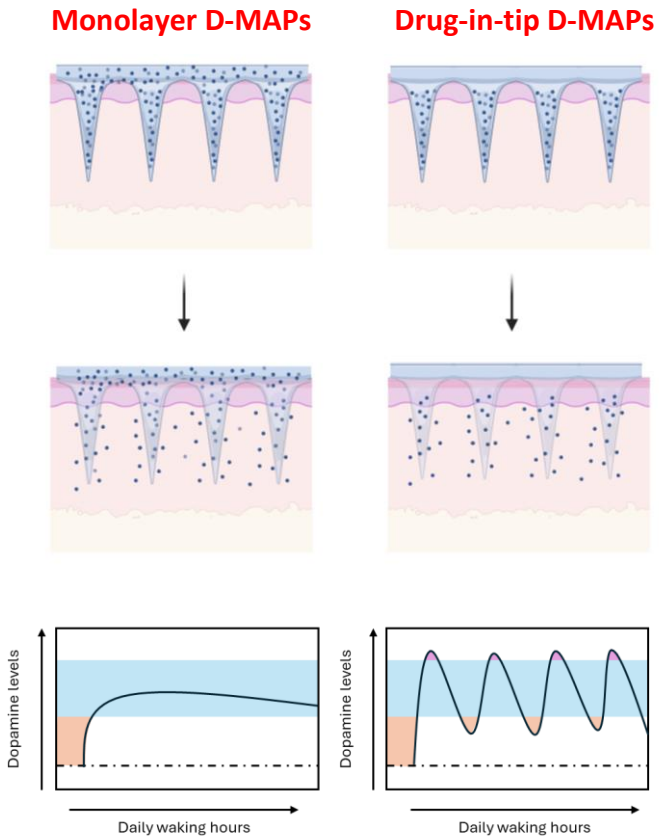


Monolayer D-MAPs



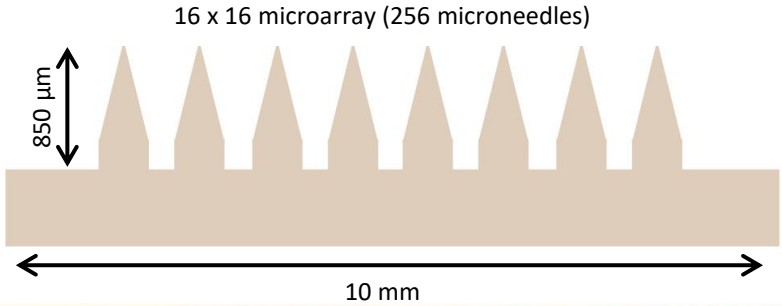
- Drug

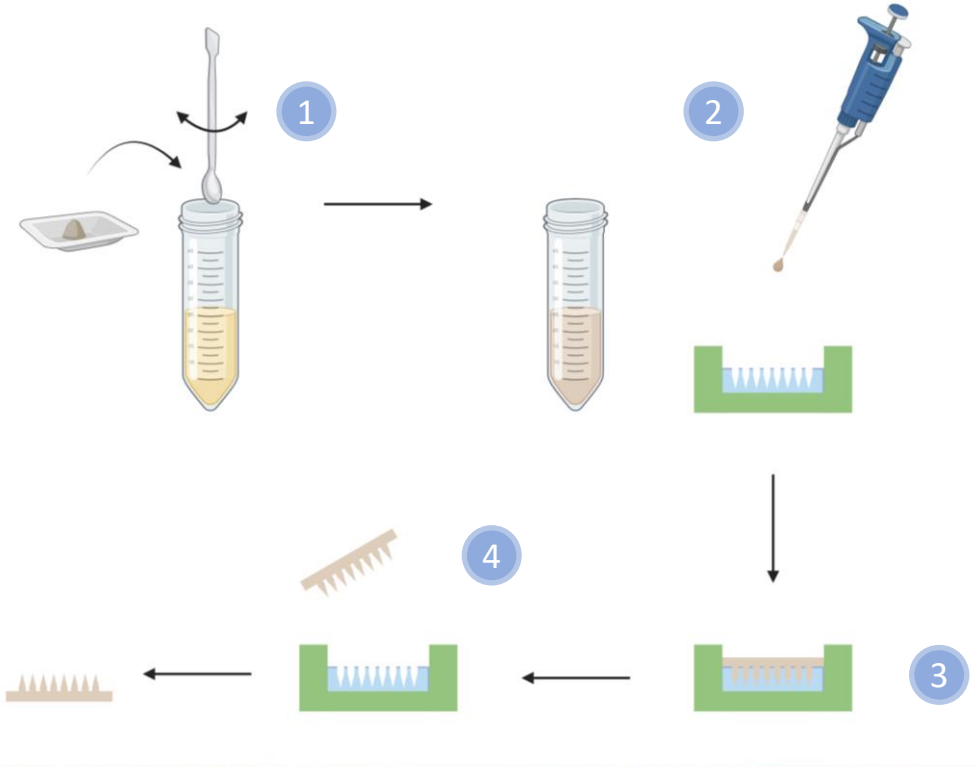
- Water-soluble polymer



Monolayer D-MAPs: Fabrication *via* aqueous micromoulding

1. APO dissolved in aqueous solution of poly(vinyl alcohol), poly(vinyl pyrrolidone) and ascorbic acid (antioxidant)
2. 500 mg of APO / PVA / PVP blend cast onto negative 16 x 16 microarray moulds. Centrifuged at 4000 rpm for 20 minutes
3. Dried at ambient temperature for 48 hours
4. MAP demoulded, trimmed into square 10 x 10 mm area and fully dried at 37 °C for 24 hours



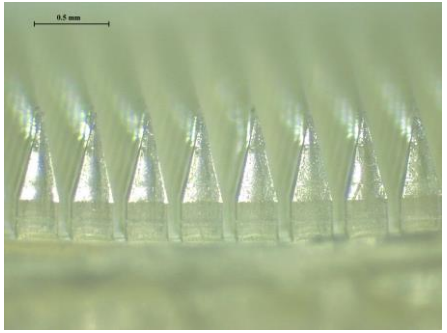
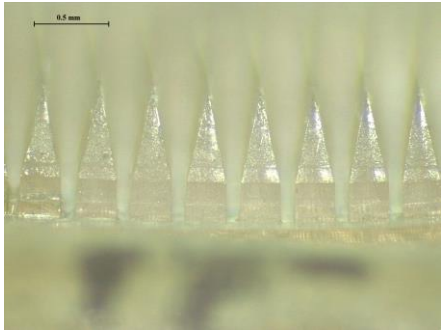
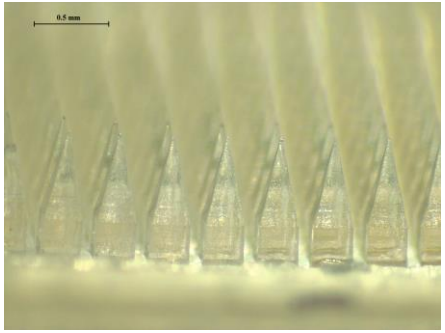
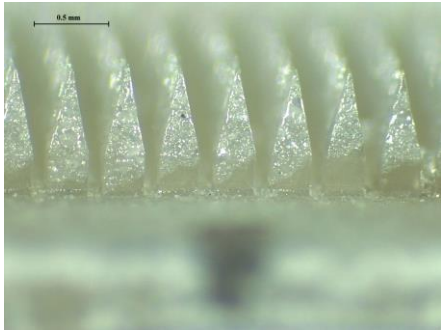
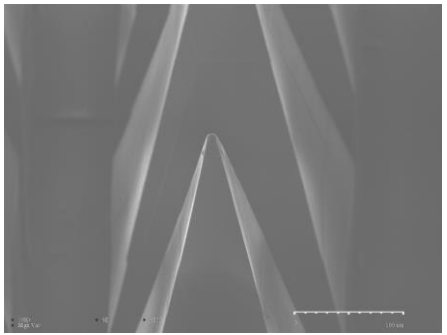
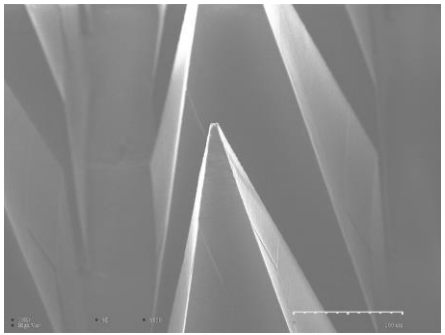
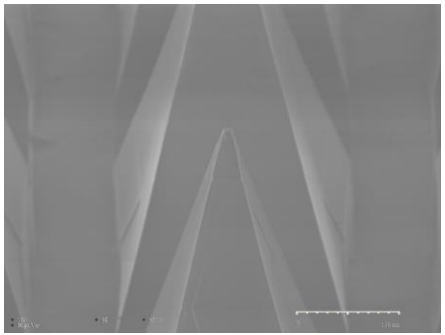
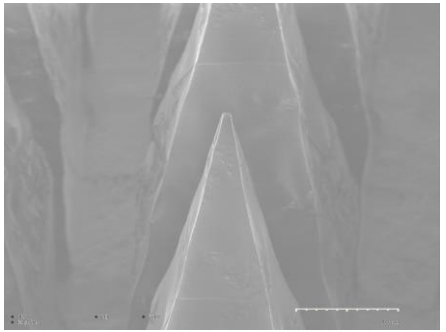


Monolayer D-MAPs: Blend Compositions

Formulation	APO (% w/w)	[a] PVA (% w/w)	[b] PVP (% w/w)	Ascorbic acid (% w/w)	H_2O (% w/w)
1.0% APO	1.00	18.75	18.75	5.00	56.50
2.5% APO	2.50	18.00	18.00	5.00	56.50
5.0% APO	5.00	16.75	16.75	5.00	56.50
10.0% APO	10.00	14.25	14.25	5.00	56.50

[a] *Molecular weight:* ***9 – 10 kDa, 13 – 23 kDa*** *or* ***31 – 50 kDa***
[b] *Molecular weight:* ***58 kDa***

Monolayer D-MAPs: Morphology

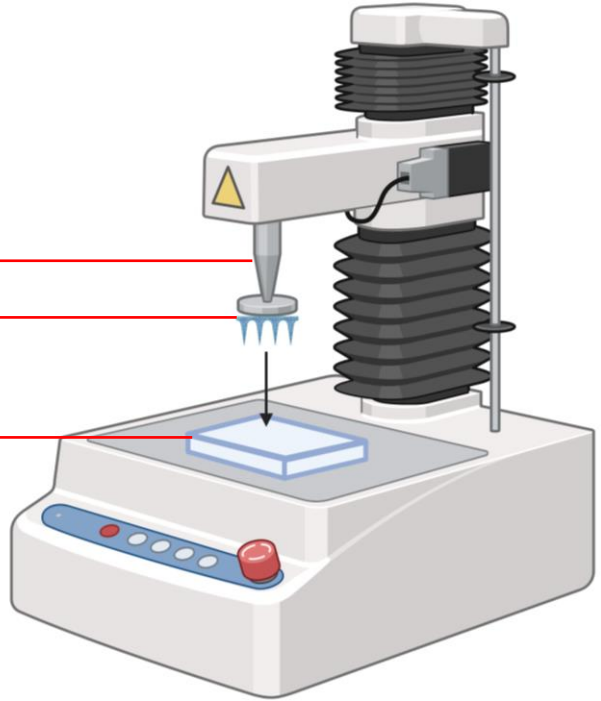
1.0% APO	2.5% APO	5.0% APO	10.0% APO
			
			

Monolayer D-MAPs: Compression Testing

Adjustable probe (applies force)

MAP

Aluminium block OR Parafilm® M (in vitro skin model)



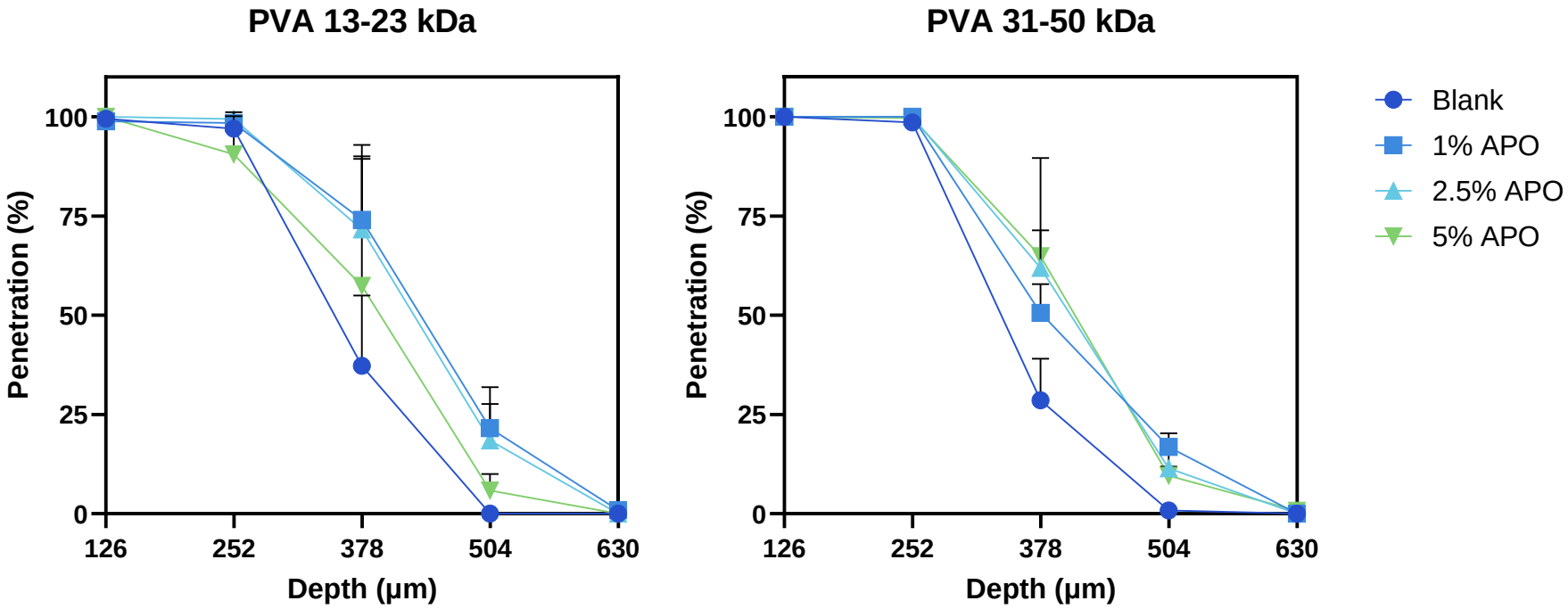
Monolayer D-MAPs: Parafilm®M Insertion

APO (% w/w)	PVA 9 – 10 kDa	PVA 13 – 23 kDa	PVA 31 – 50 kDa
1.00	✓	✓	✓
2.50	✗	✓	✓
5.00	✗	✓	✓
10.00	✗	✗	✗

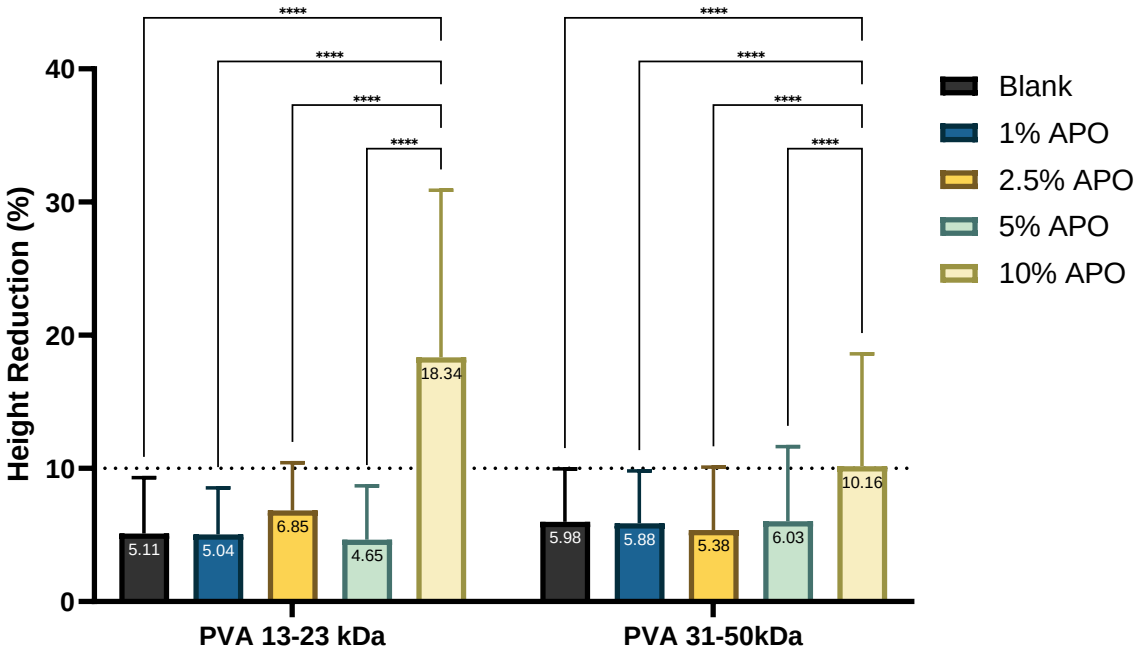
✗ *- >2 out of 3 replicates fractured under compression of 32 N for 30 s*

✓ *- <1 out of 3 replicates fractured under compression of 32 N for 30 s*

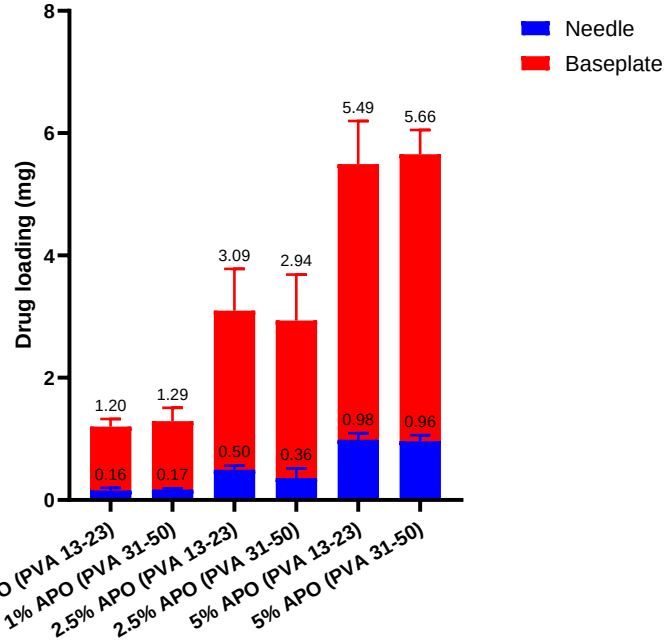
Monolayer D-MAPs: Parafilm®M Insertion



Monolayer D-MAPs: Mechanical Integrity



Monolayer D-MAPs: Drug Content



1.0% APO = ~ *1.2 – 1.3 mg*

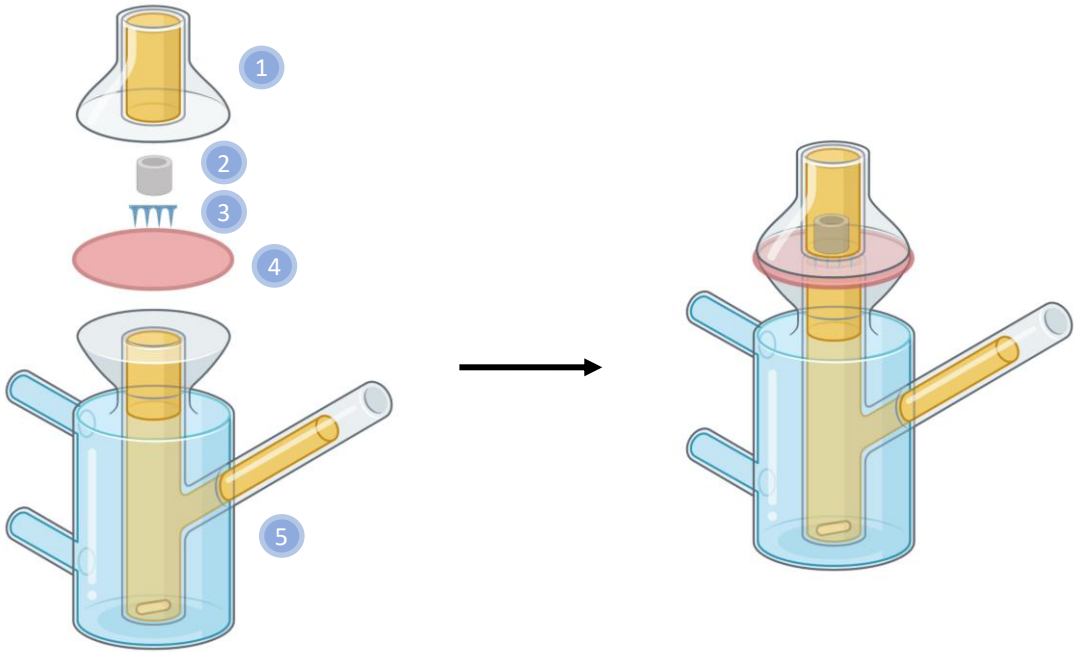
2.5% APO = ~ *2.9 – 3.1 mg*

5.0% APO = ~ *5.5 – 5.7 mg*

~12 - 18% drug loading localised in the needle tips

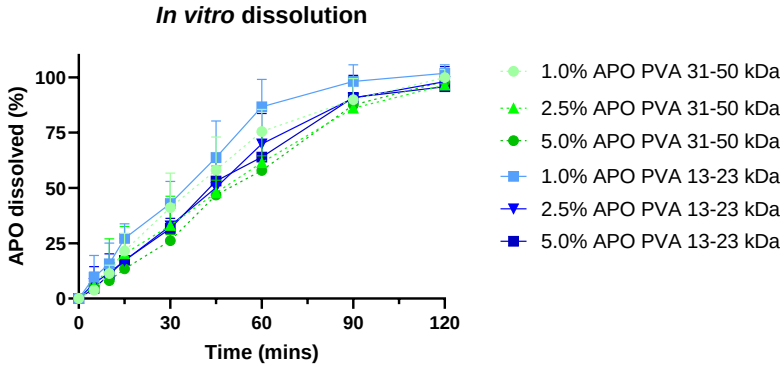
Monolayer D-MAPs: *Ex vivo* studies

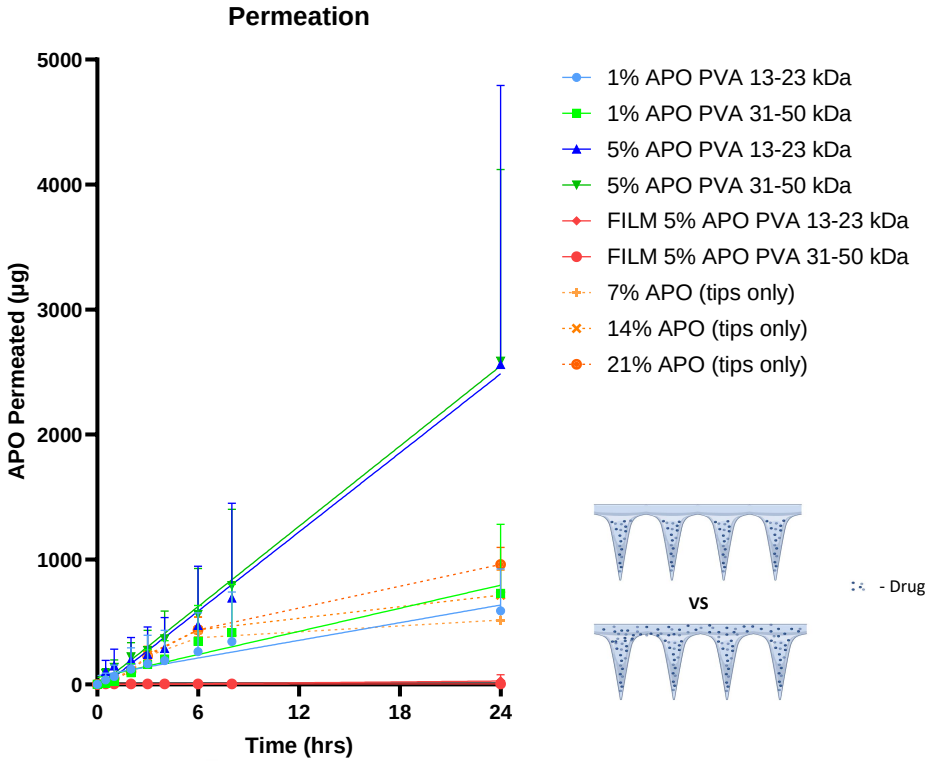
1. Donor cell
2. Stainless steel weight
3. MAP; *inserted with manual pressure for 30 s*
4. Dermatomed neonatal porcine skin; *~ 350 µm in thickness*
5. 12 mL receptor compartment; *containing PBS (pH 7.4) + 0.1% (w/w) ascorbic acid; thermostated at 37.4 °C via water jacket*



Monolayer D-MAPs: *Ex vivo* permeation

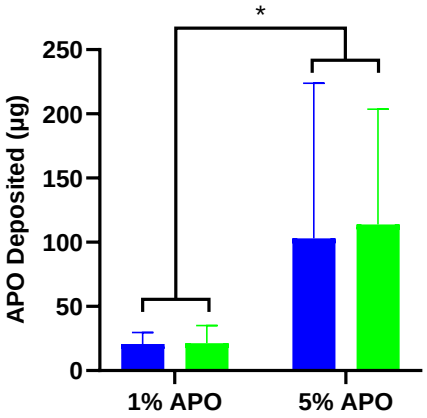
- After dissolution of tips, baseplate acts as a reservoir maintaining **zero order flux**
- **No difference in flux** between low and high MW PVA due to similar dissolution profile
- Dissolution of APO the **rate-limiting step**



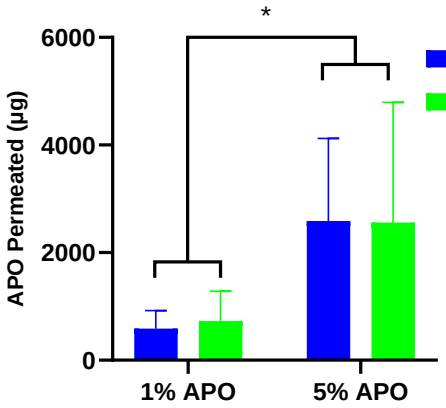


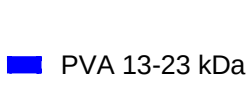
Monolayer D-MAPs: *Ex vivo* delivery efficiency

Deposition

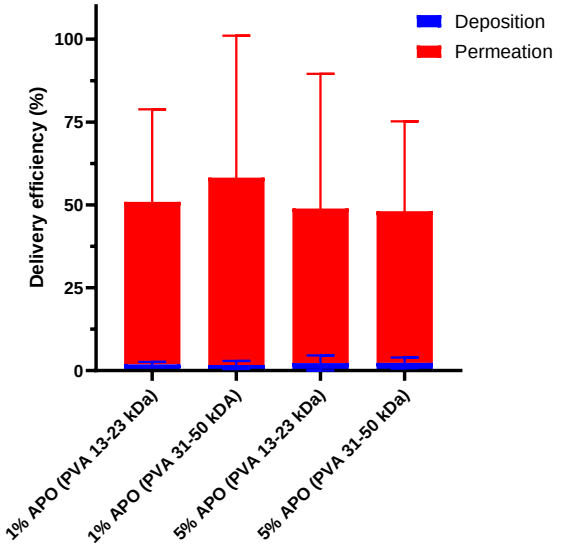


Permeation





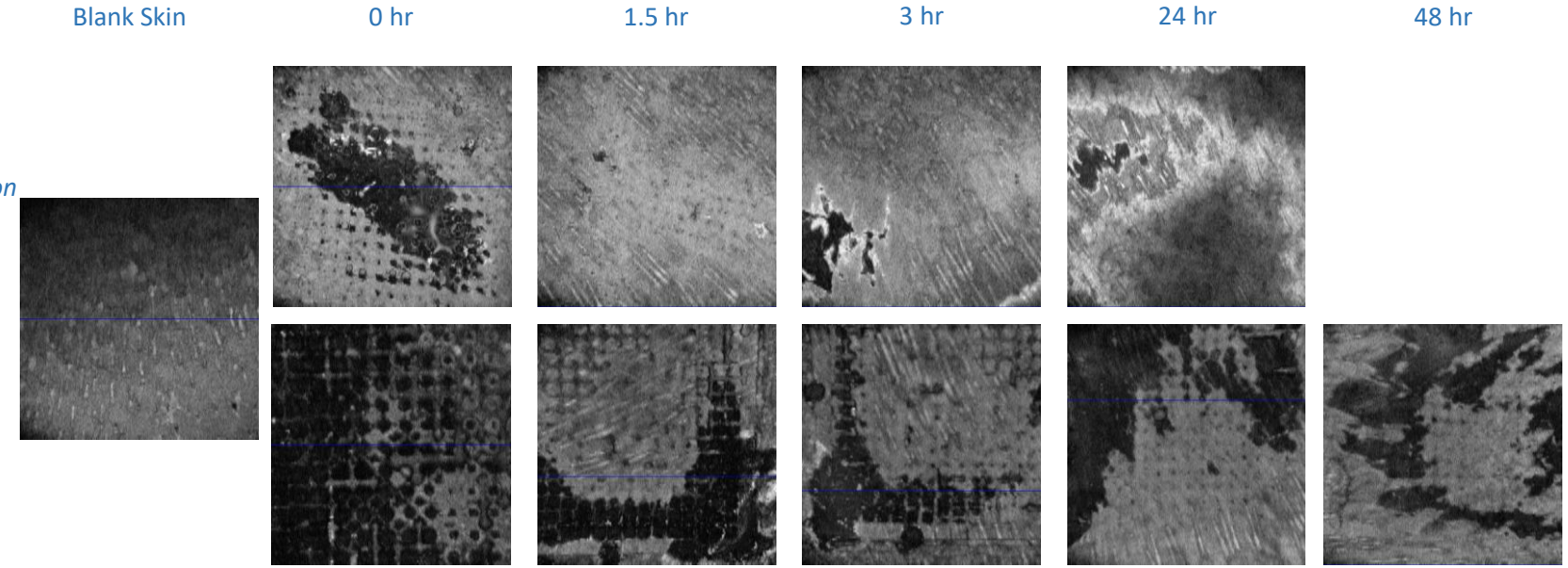
Delivery Efficiency



*Two-way ANOVA; main row effect, * $p < 0.05$*

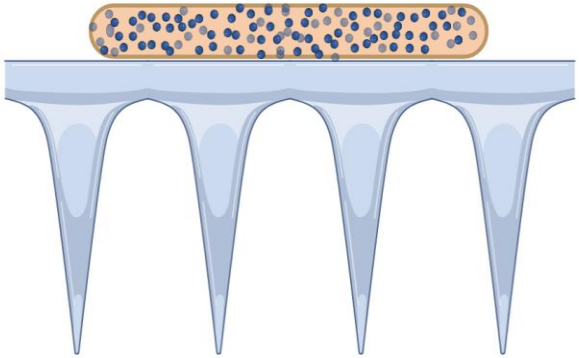
APO not fully delivered; permeation likely to maintain with continued patch wear-time

Monolayer D-MAPs: Optical Coherence Tomography



Baseplate maintains occlusive conditions; pores remain open for up to 48 hours, confirms potential for sustained release for > 24 hours

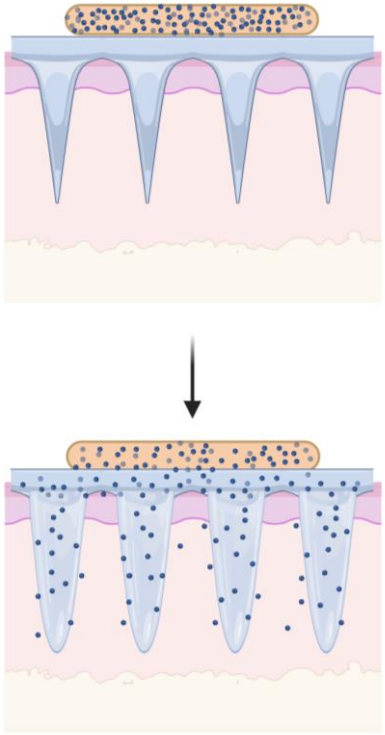
Hydrogel-forming Microarray Patches (HF-MAPs)



- Drug

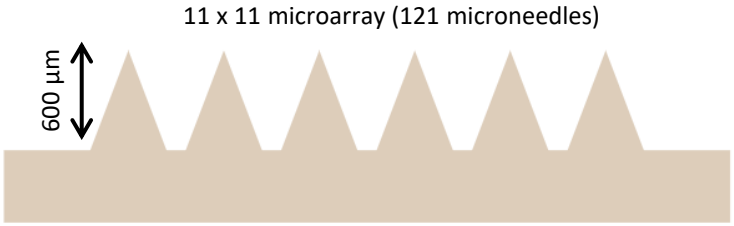
- Drug reservoir

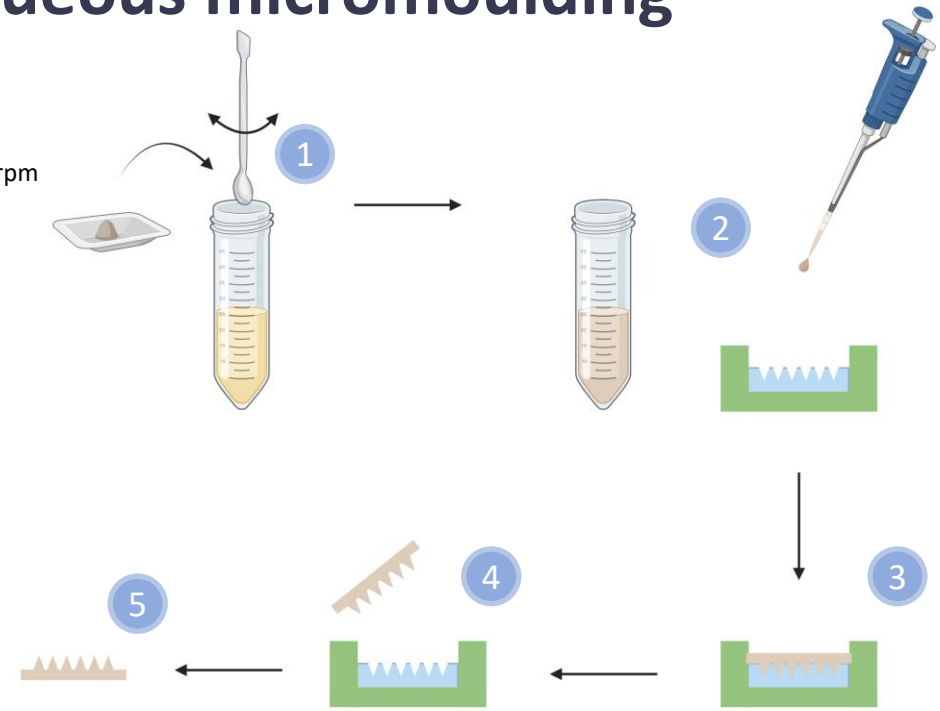
- Crosslinked polymeric network



HF-MAPs: Fabrication *via* aqueous micromoulding

1. Prepared aqueous solution of polymer (PVA, PVP or poly(vinylmethylether-co-maleic acid) (PMVA) and crosslinker (citric acid or poly(ethylene glycol) (PEG))
2. Casted 500 uL onto negative 11 x 11 microarray moulds. Centrifuged at 3500 rpm for 15 minutes
3. Dried at ambient temperature for 48 hours
4. MAP demoulded, trimmed and fully dried at 37 °C for 24 hours
5. MAP thermally crosslinked for set period of time at a set temperature



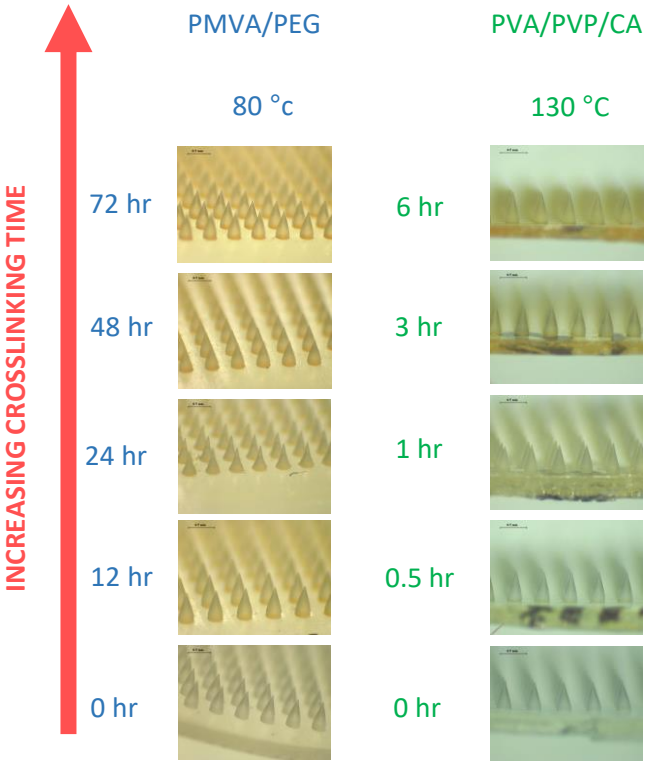


HF-MAPs: Aqueous Blend Compositions

Formulation	[a] PVA (% w/w)	[b] PVP (% w/w)	[c] PMVA (% w/w)	Citric acid (% w/w)	[d] PEG (% w/w)	H_2O (% w/w)
PVA/PVP/CA	15	10	-	1.5	-	73.5
PMVA/PEG	-	-	20	-	7.5	72.5

[a] *Molecular weight:* ***85 – 124 kDa***
[b] *Molecular weight:* ***58 kDa***
[c] *Molecular weight:* ***1500 kDa***
[d] *Molecular weight:* ***10 kDa***

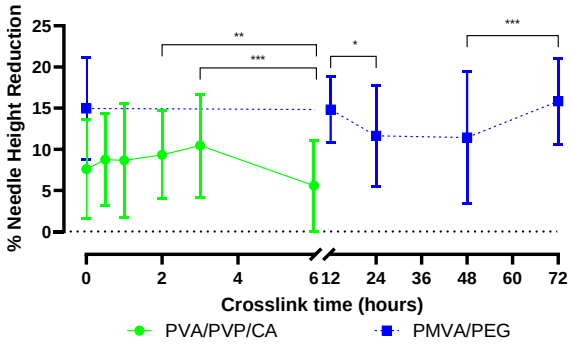
HF-MAPs: Characterisation and Morphology



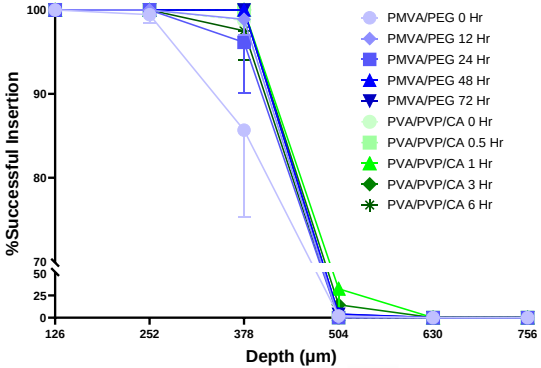
Across a range of crosslinking times, both MAP formulations perform well mechanically and insert well into an *in vitro* Parafilm® M skin model

COMPRESSION TESTING

Microneedle Height Reduction

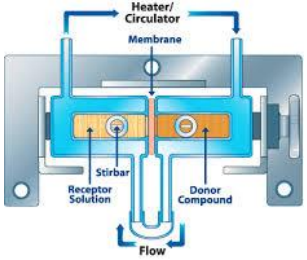


Parafilm® M Insertion



HF-MAPs: Permeability of APO *via* Solute Diffusion

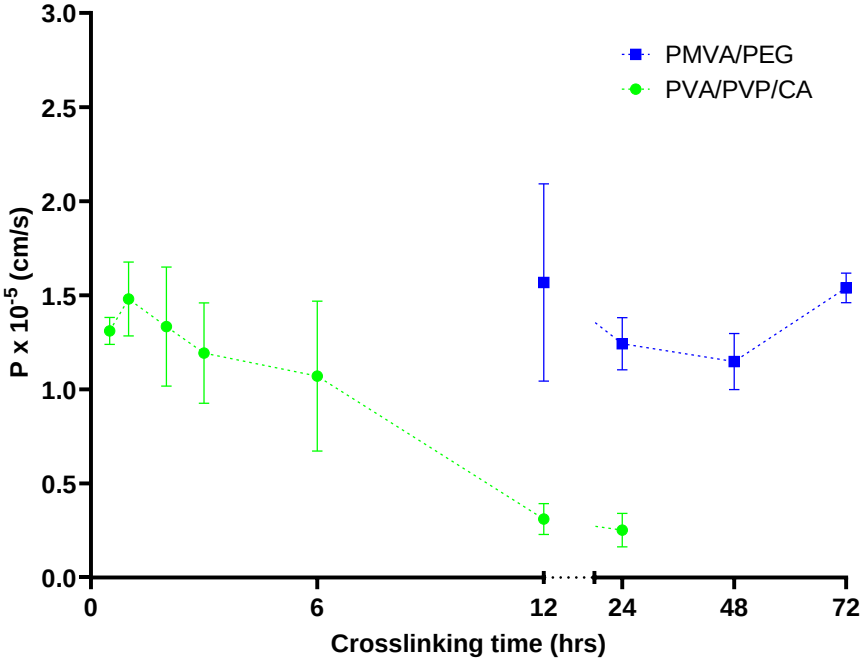
10 x 10 mm hydrogel films fully swollen in PBS (pH 7.4) + 0.1% (w/w) ascorbic acid and used as permeation membrane



$$\ln\left(1-\frac{2C_t}{C_0}\right)=-\frac{2A}{V}Pt$$

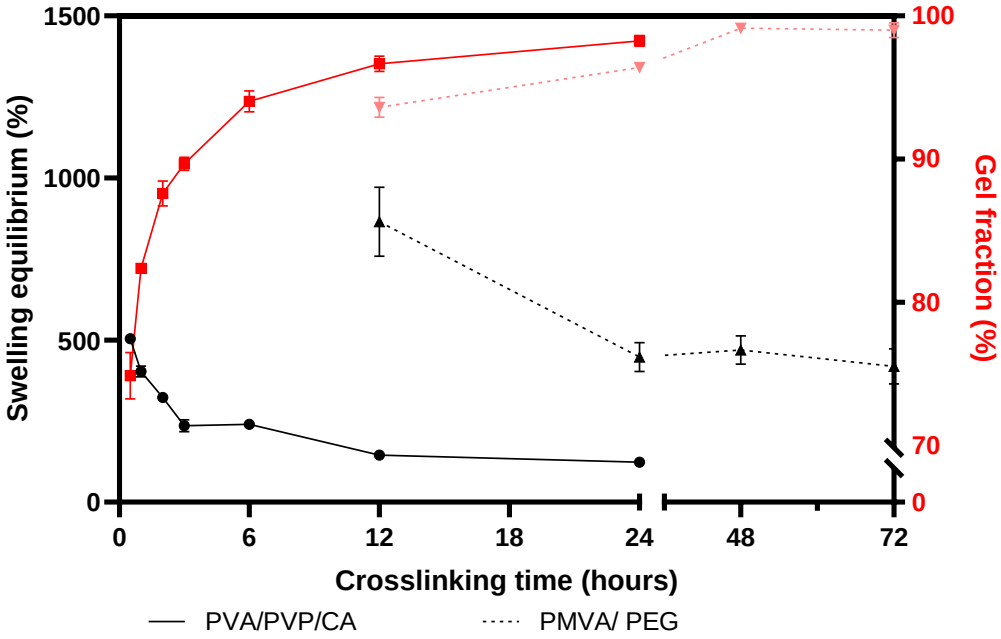
C_t = cumulative concentration of APO at time t (ug/cm^3)
C_0 = initial concentration of APO in donor compartment (ug/cm^3)
V = volume of receptor compartment (cm^3)
A = effective area of permeation (cm^2)
P = permeability coefficient (cm/s)

Permeability Coefficient *vs* Crosslinking time

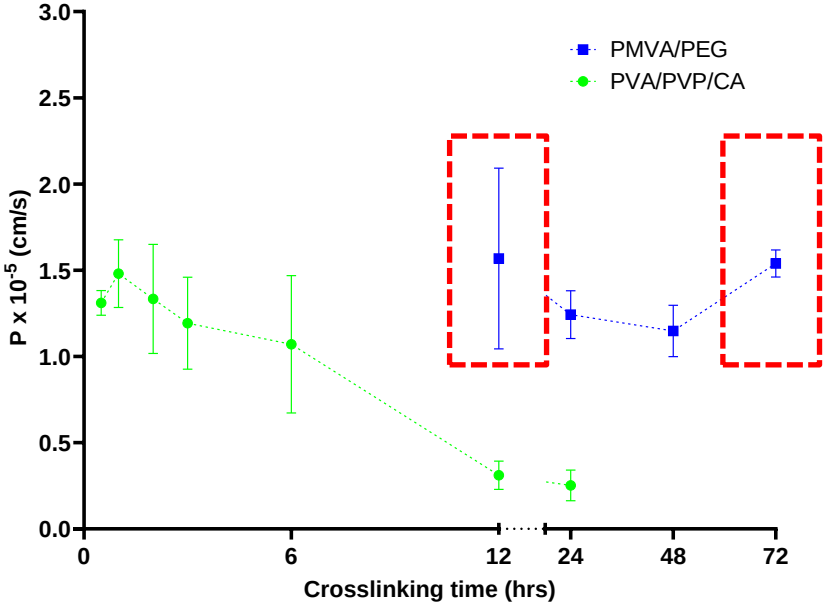


HF-MAPs: Formulation selection

Swelling Equilibrium / Gel Fraction *vs* Crosslinking time

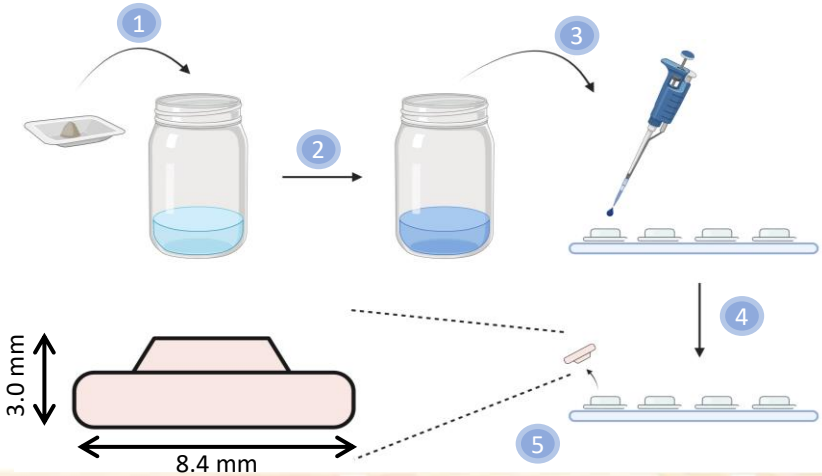


Permeability Coefficient *vs* Crosslinking time



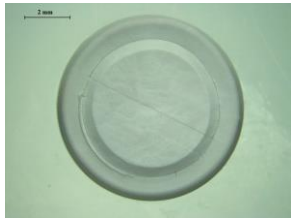
HF-MAPs: APO Lyophilised Wafers

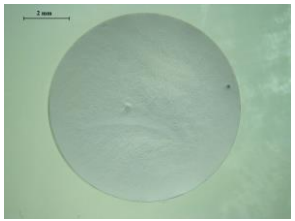
1. 20% (w/w) APO mixed in aqueous blend of 7.5 – 45% (w/w) mannitol, 2% (w/w) gelatin, 1% (w/w) ascorbic acid
2. Dual-asymmetric centrifugation 3500 rpm for 3 minutes with X5 3.0 mm zirconium beads. Sonicated for 2 hours
3. 150 mg aliquots cast into 8 x 4 mm cylindrical moulds
4. Frozen at -80 °C. Lyophilised *via* 700 minutes primary drying (-40 °C to -10 °C) and 750 minutes secondary drying (0 °C to 20 °C)
5. Wafers demoulded and stored in dessicated conditions

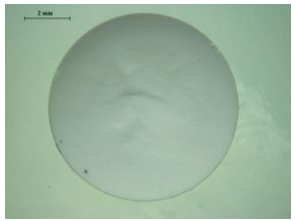


15% Mannitol

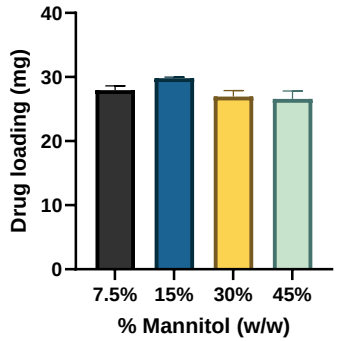
30% Mannitol



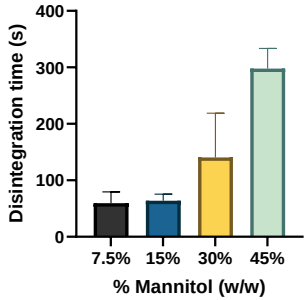




Drug loading

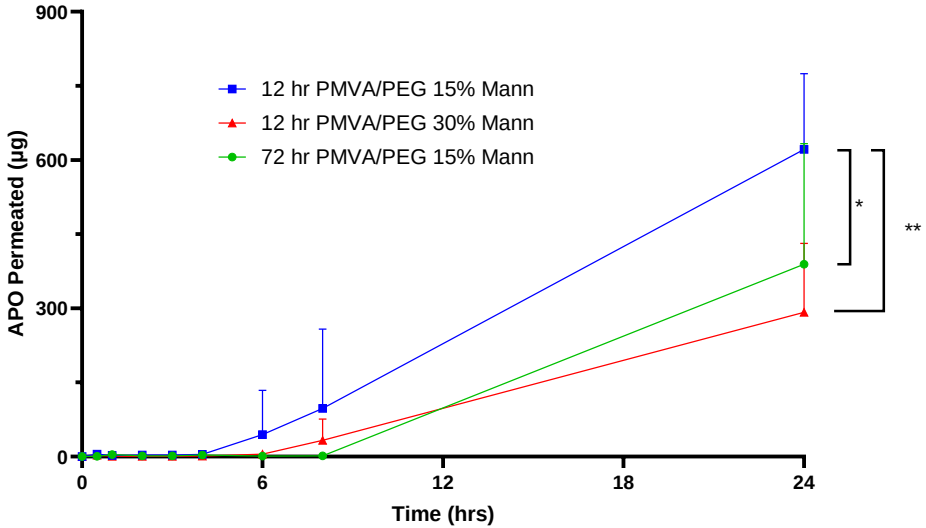


Disintegration Time

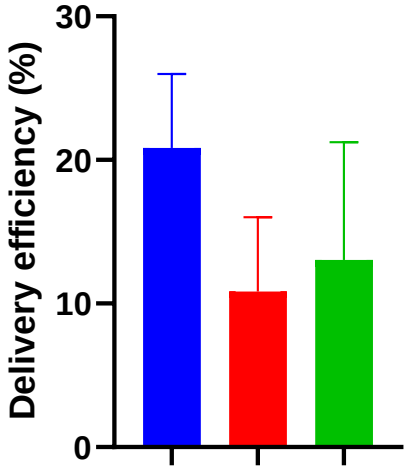


HF-MAPs: *Ex vivo* permeation and delivery efficiency

Permeation over 24 hours



Reservoir Delivery Efficiency



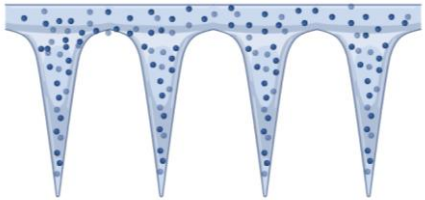
Zero order flux achieved after **4 – 8 hour lag-time**; may be maintained for **several days**

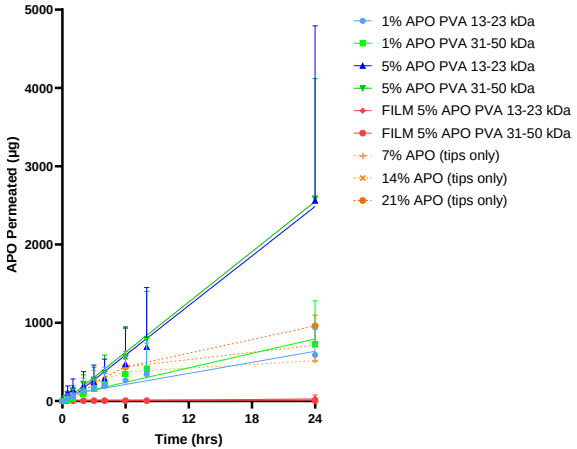
- <20% of reservoir delivered

To summarise…

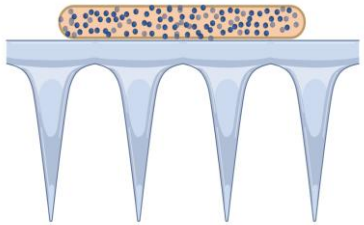
AIM:

Design and characterise novel D-MAP and HF-MAP systems for sustained transdermal release of APO



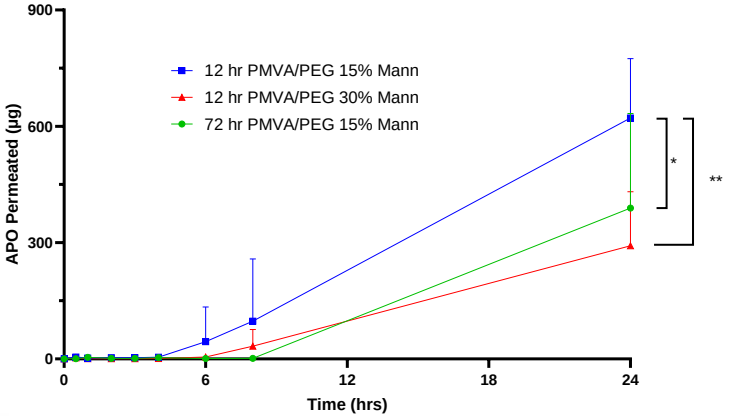


- ✓ Achieved range of ***ex vivo* transdermal flux** of APO over a 24-hour period; **significantly greater than current literature**



- ✓ Based entirely on **passive diffusion**; no mechanism of facilitated delivery *BAR* the microneedle

- ✓ Easy and reproducible administration



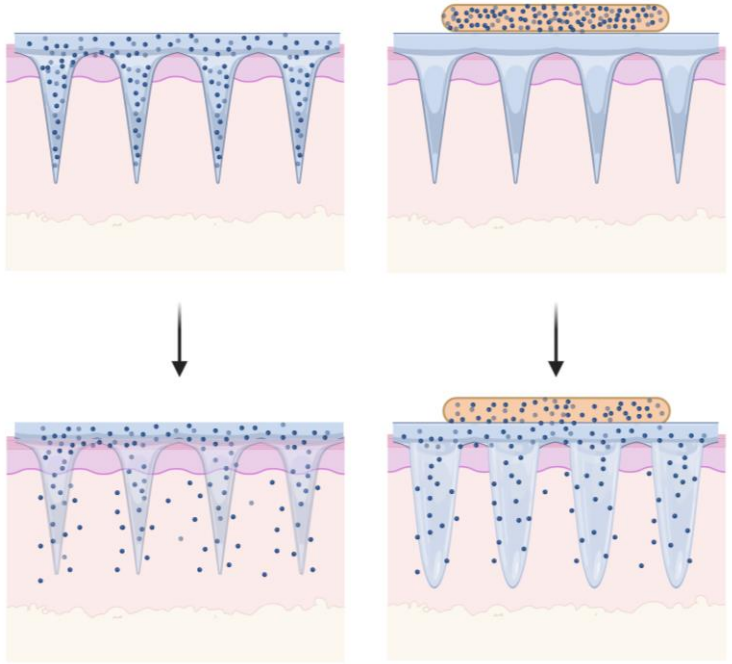
Future outlook

Preclinical studies

- *In vivo* pharmacokinetics

Further study

- End-user / patient perspectives




een's University Belfast – School of Pharma
RAMONES

Thank you for listening!

Questions?