Quality by design guided development of hydrogel-forming microneedle array patches for enhanced transdermal delivery of enfuvirtide

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NEXT-GENERATION DELIVERY INNOVATIONS

➢ Overview

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- Hydrogel-forming microneedle array patch (HMAP): Chemically crosslinked micron-scale needles from polyers in micromoulds.
- Reservoir: Lyophilised wafer containing drug with excipients.

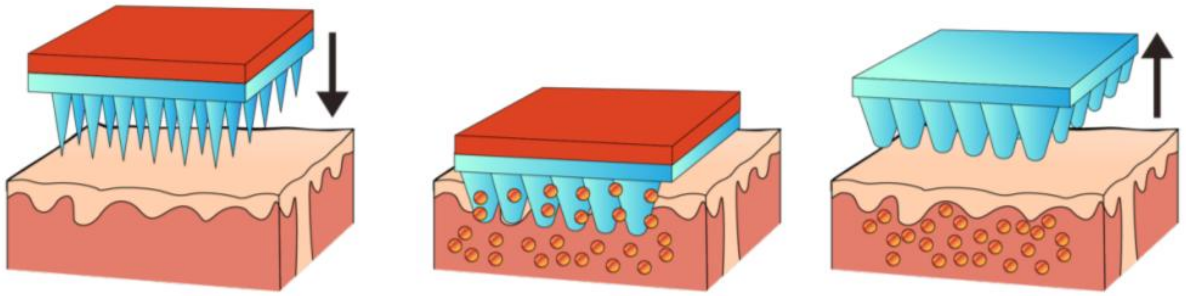


Figure 1. HMAP application in combination with reservoir.

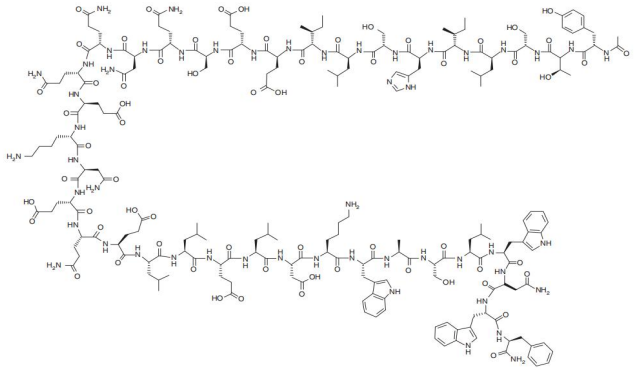
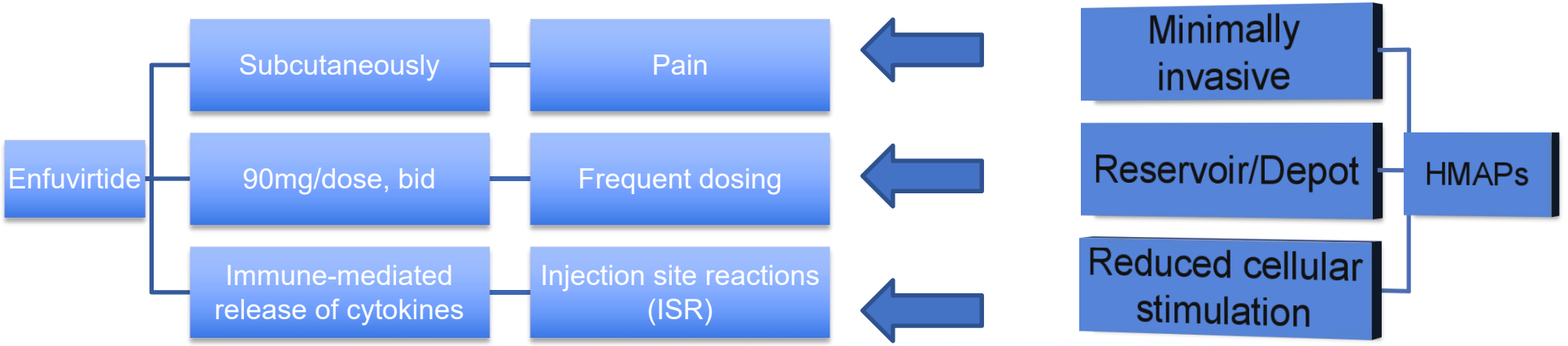


Figure 2. Chemical structure of enfuvirtide.



➢ HMAP development

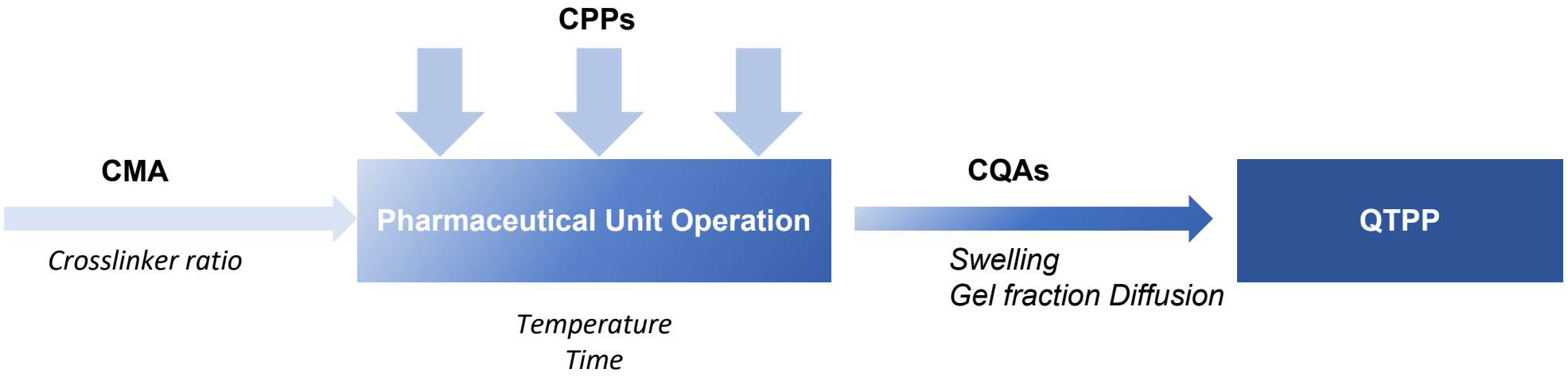


Table 1. Factors and responses in Central Composite Design.

Factors	Level			Response	Goal
	-1	0	+1		
X1= Crosslinker ratio (% w/w)	2.25	6.1	10	R1=Swelling (%)	In range
X2=Temperature (℃)	80	116.5	150	R2=Gel fraction (%)	In range
X3=Time (min)	20	48.9	80	R3=Diffusion (%)	Maximise

19 runs were suggested by the software

➢ HMAP development

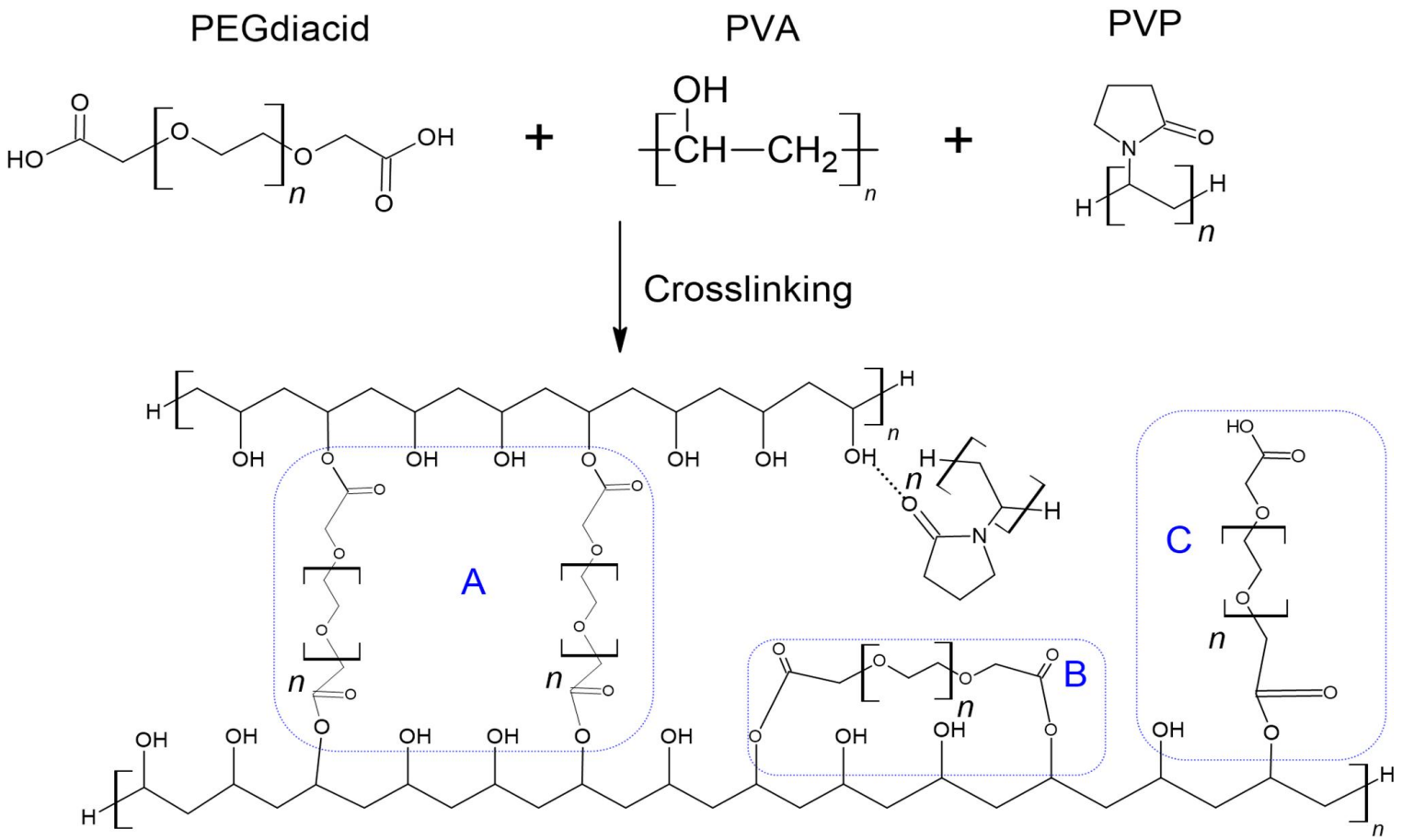


Figure 3. Proposed crosslinking reaction between PVA/PVP/PEGdiacid-based hydrogel.

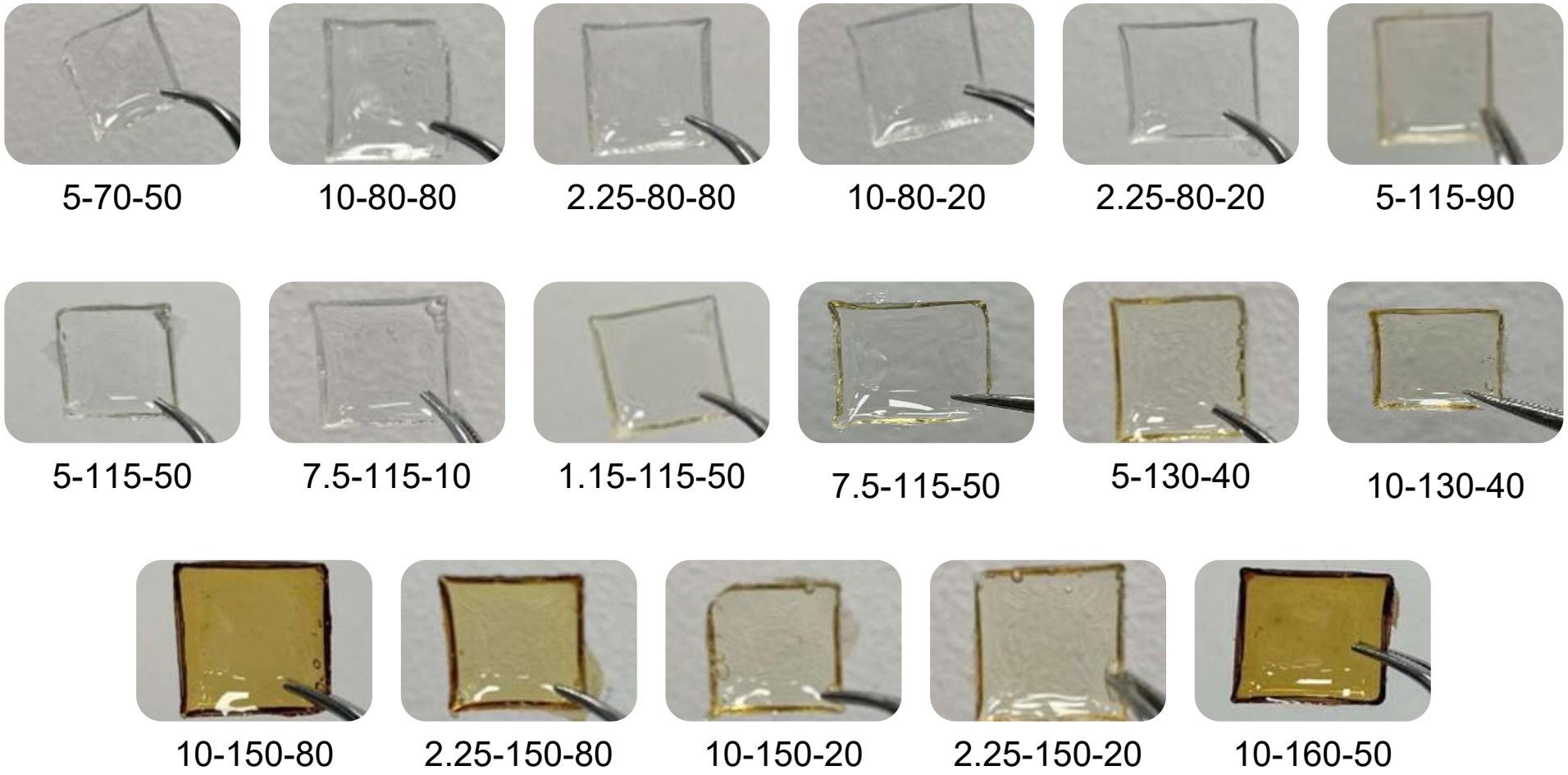
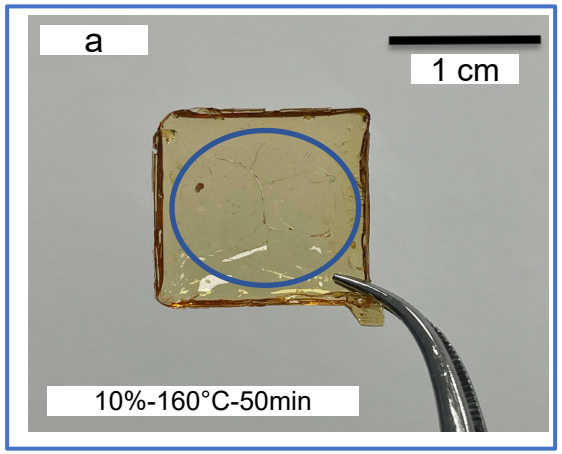
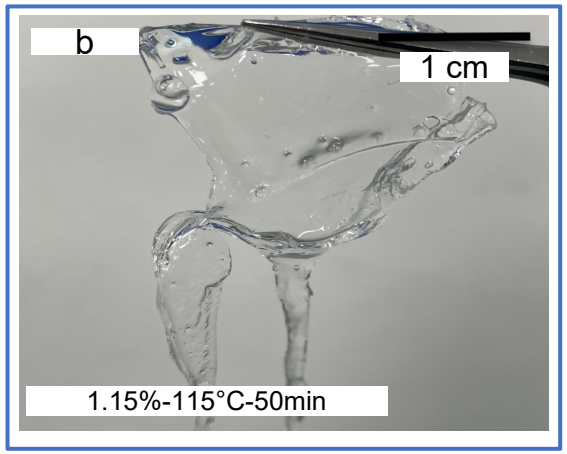
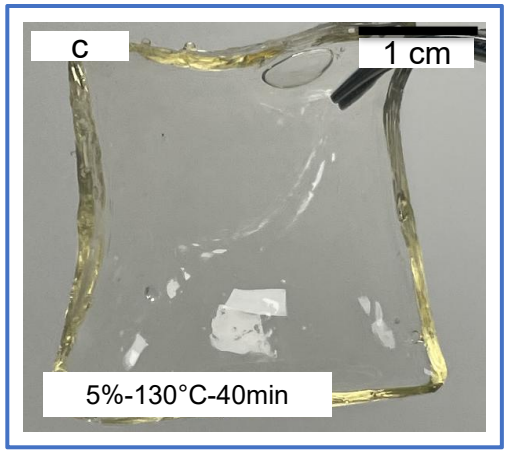


Figure 4. Hydrogel films after crosslinking expressed in crosslinker amount (%)-temperature (°C)-time (min).

➢ HMAP development







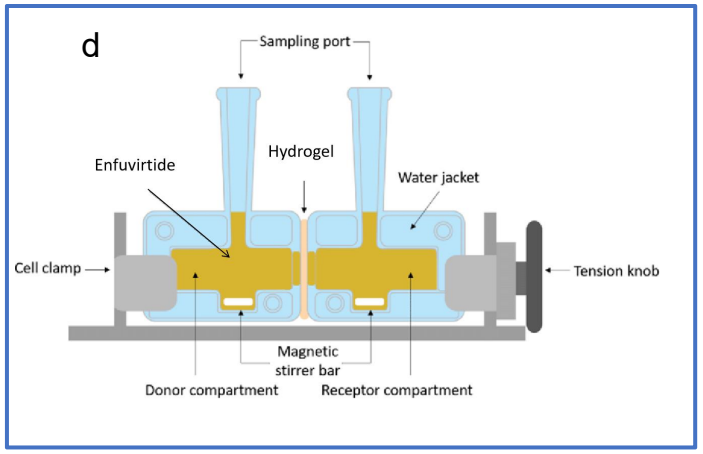


Figure 5. Examples of extremely rigid (a), extremely weak (b), normal (c) swollen hydrogel films and side-by-side horizontal diffusion cells set up for *in vitro* permeation studies (d).

➢ HMAP development

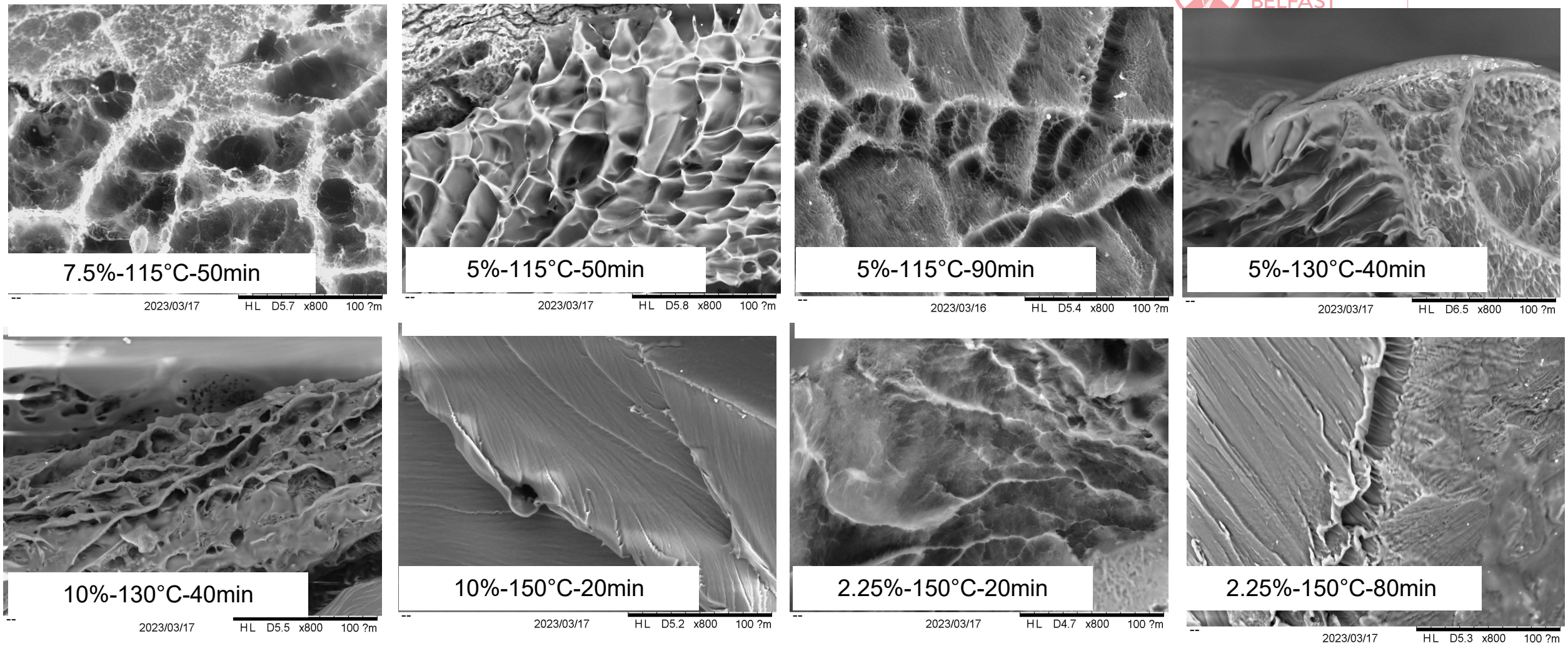


Figure 6. Cross section morphology of hydrogel films after swelling.

➢ HMAP development

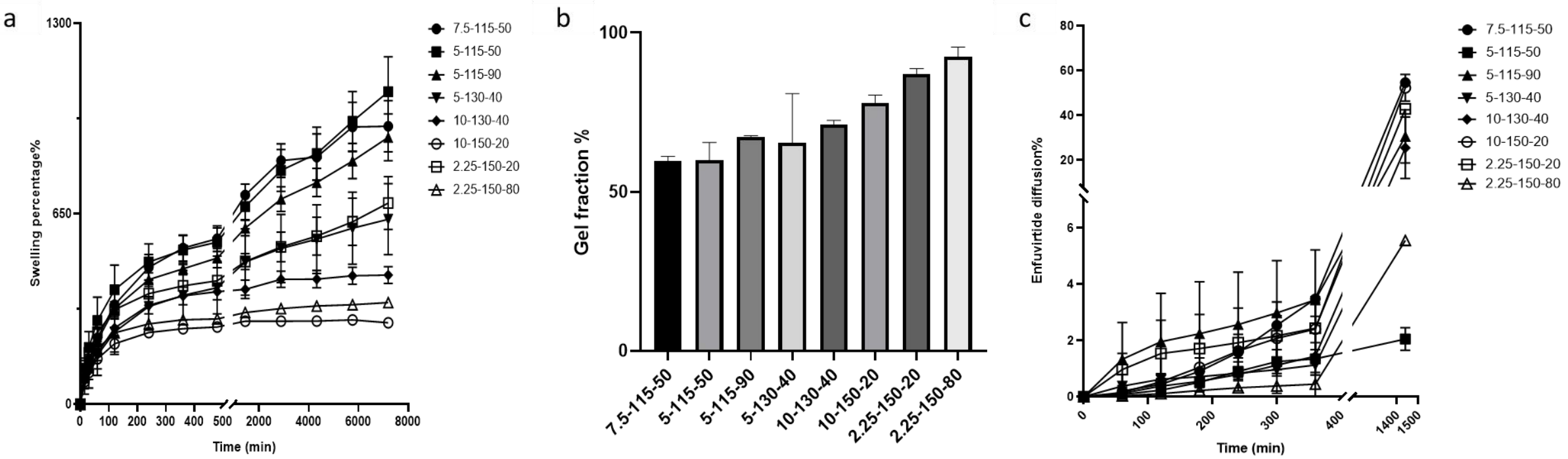


Figure 7. The swelling profile (a), gel fraction (b), and enfuvirtide diffusion percentage (c) denoted as crosslinker amount (%)-temperature (°C)-time (min) (Mean ± SD, n=3).

➢ HMAP development

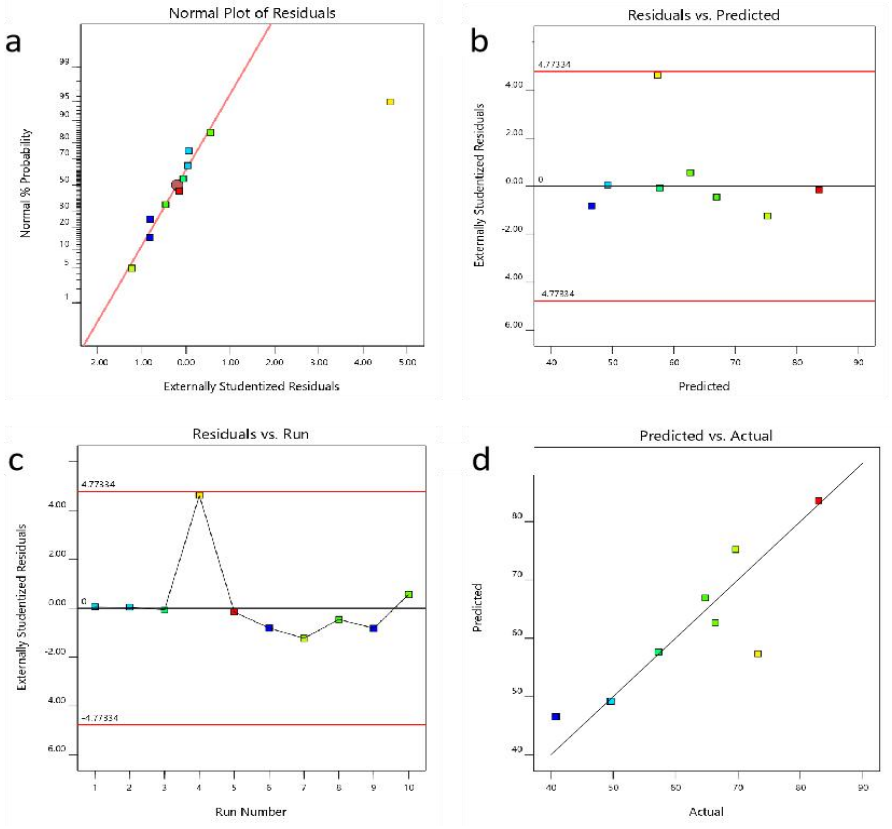


Figure 8. A diagnostics of the model for gel fraction.

Solution

Formulation with 2.25% w/w PEGdiacid crosslinked at 150℃ for 20 minutes, demonstrated the highest desirability of 0.871 and was selected for HMAP fabrication.

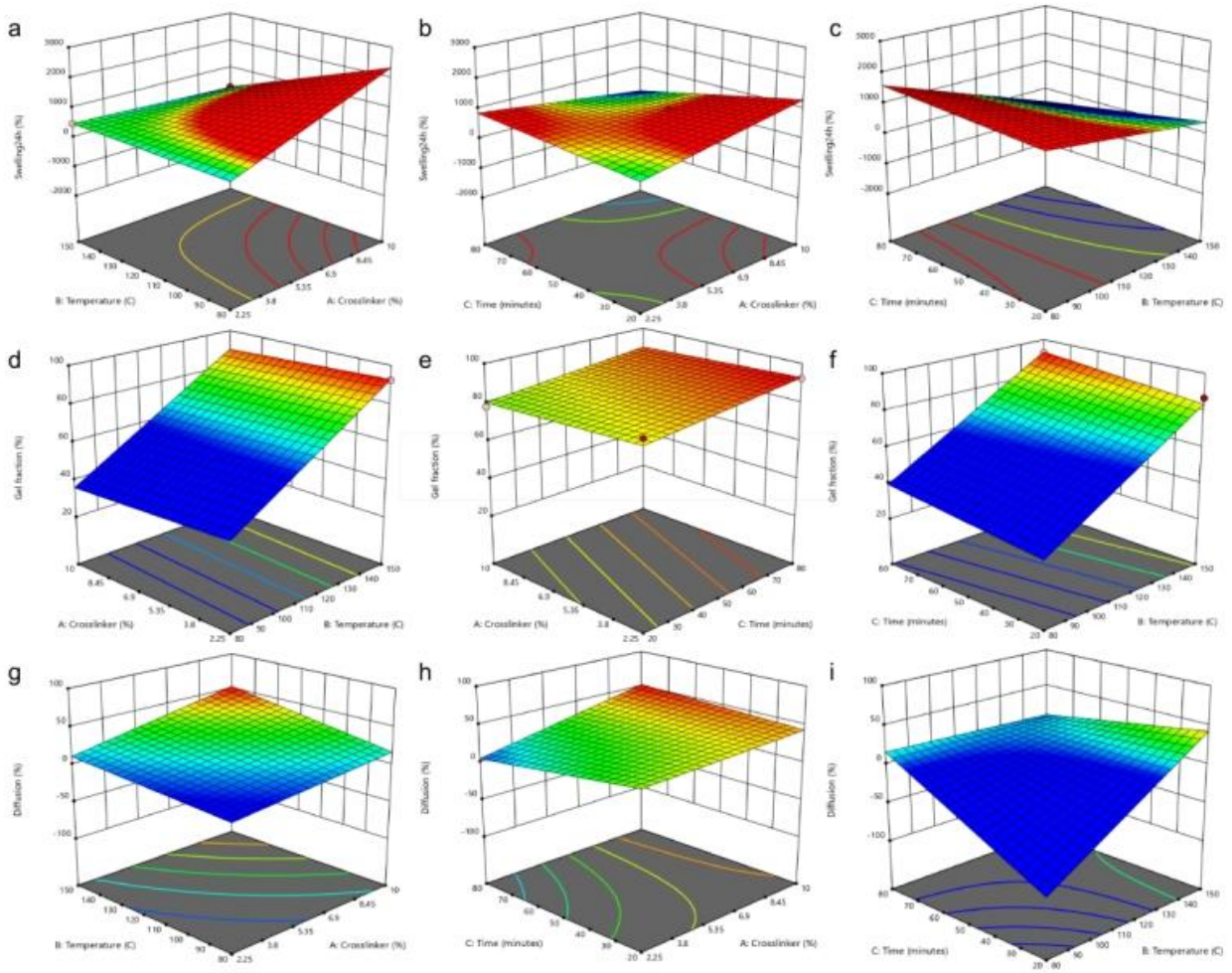


Figure 9. Response surface plots describing the effect of variables on the 24h swelling percentage (a, b, c) and gel fraction (d, e, f) and enfuvirtide diffusion across hydrogels (g, h, i).

➢ HMAP fabrication

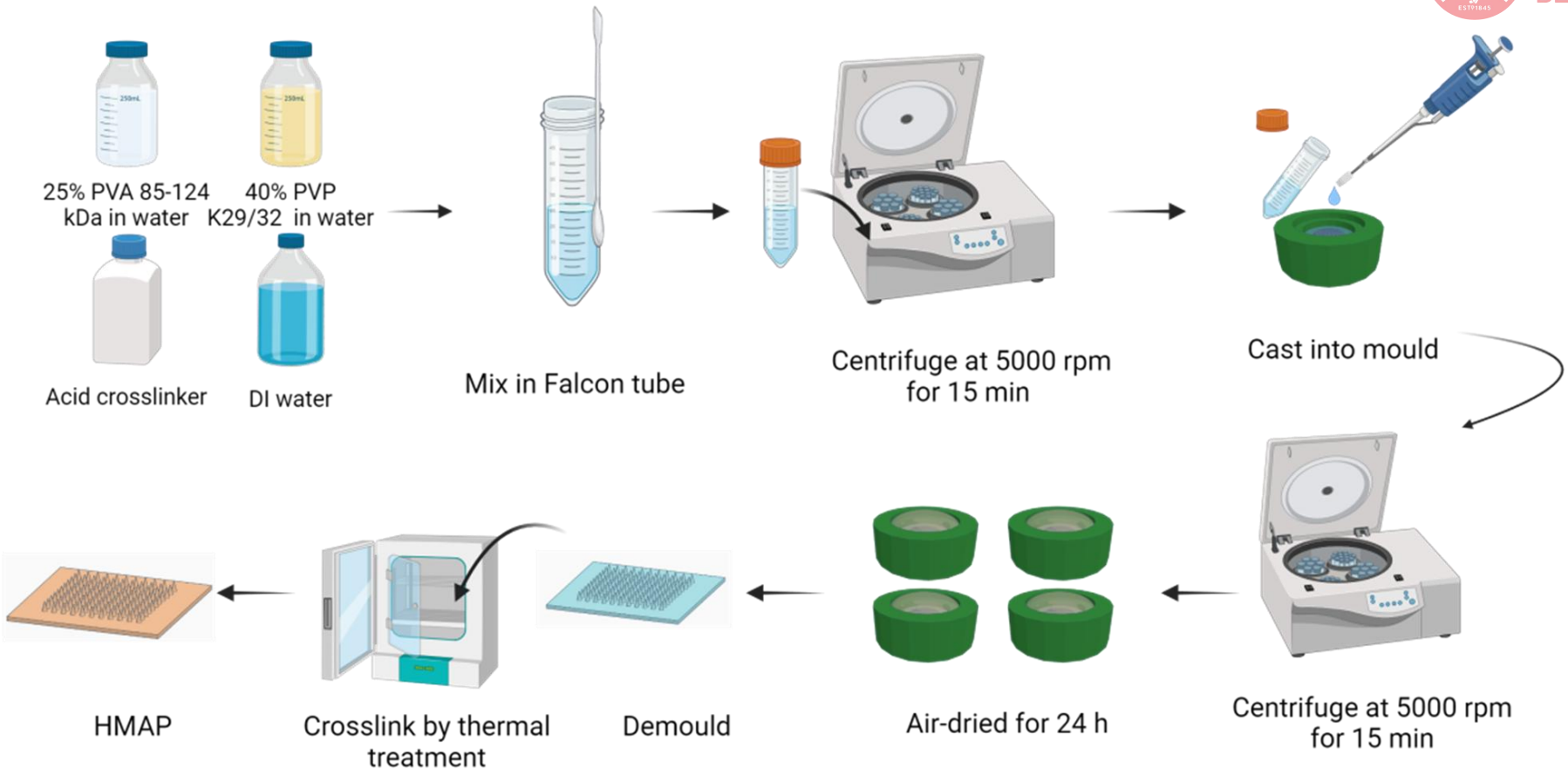


Figure 10. Schematic illustration for HMAP fabrication.

➢ HMAP characterisation

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Table 2. Summery of HMAP moulds geometry.

Geometry	Shape	Height	Interspacing	Base width
11*11	Conical	600 µm	300 µm	300 µm
14*14	Pyramidal	600 µm	250 µm	450 µm

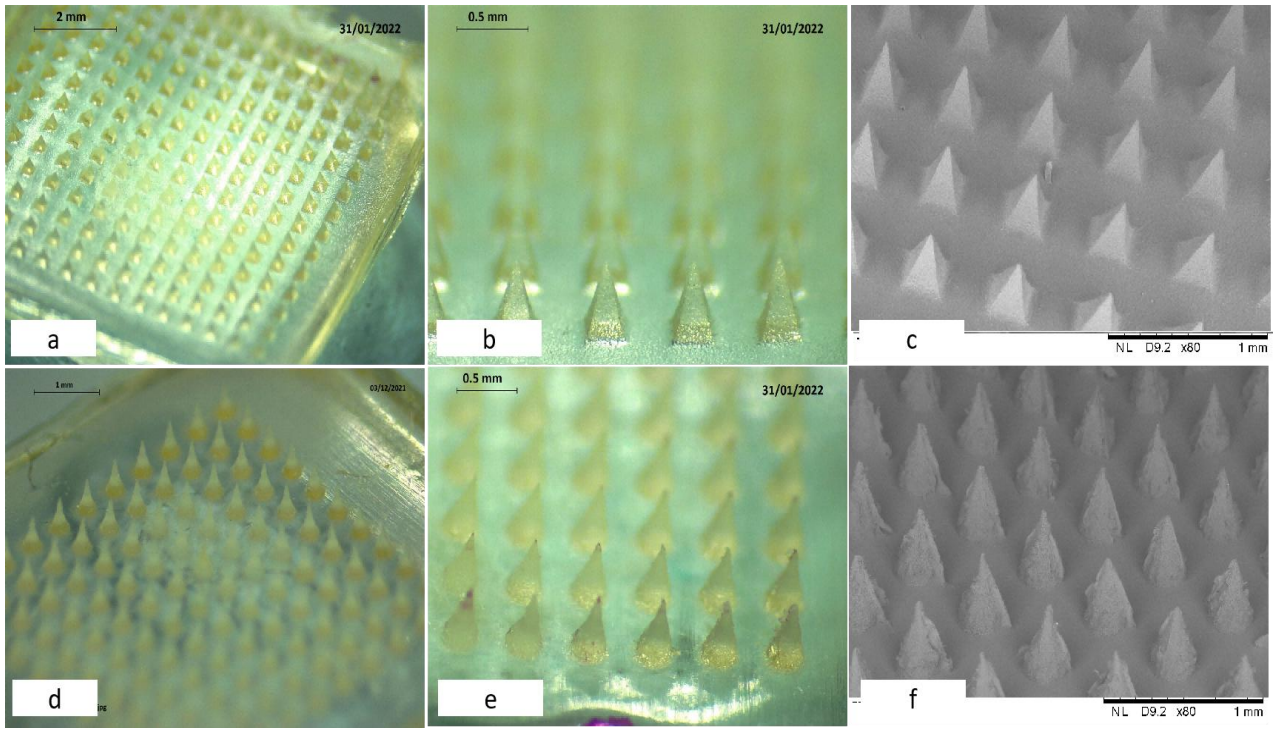

Figure 11. Morphology of HMAPs.

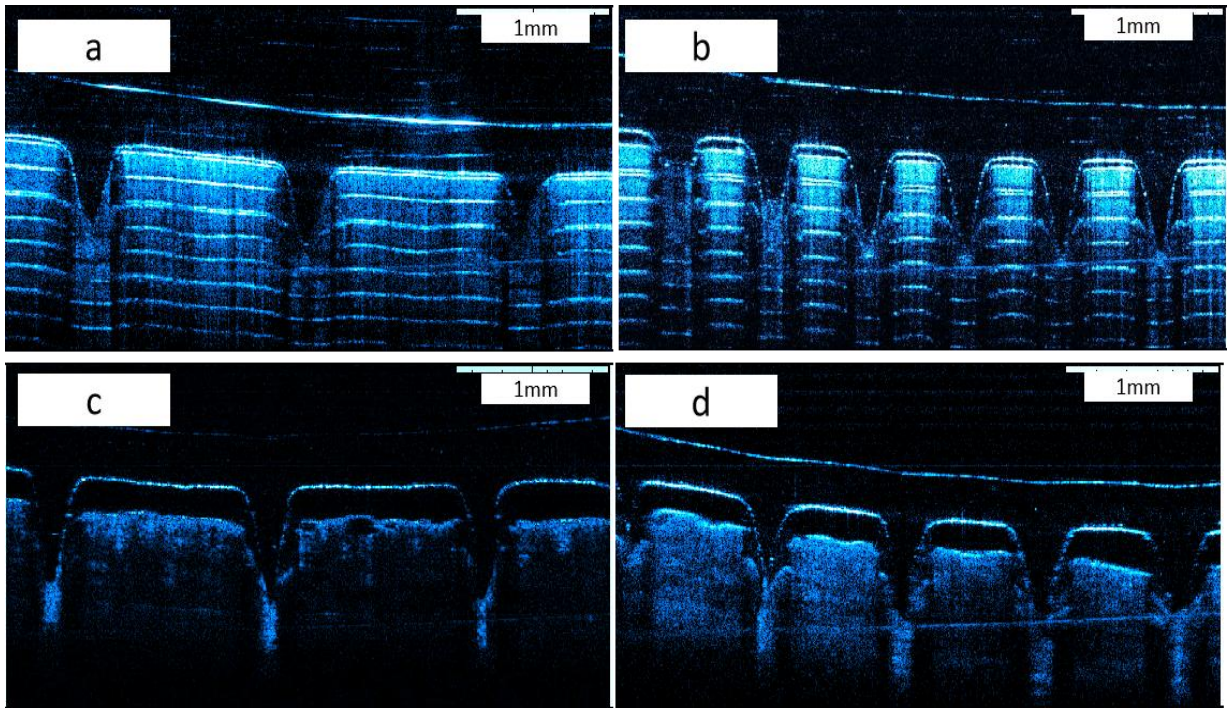

Figure 12. Insertion ability of HMAPs through Parafilm and pig skin.

➢ Reservoir development

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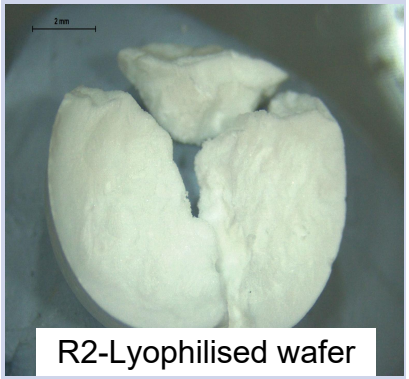
Table 3. Summery of reservoir development.

Reservoir ID	R1	R2	R3	R4	R5
Enfuvirtide % w/w	5	5	5	5	5
Mannitol % w/w	90	10	2.5	2.5	2.5
Gelatin % w/w	5	5	5	2.5	1.25
Water % w/w	0	80	87.5	90	91.25
Morphology	 R1-Compressed tablet	 R2-Lyophilised wafer	 R3-Lyophilised wafer	 R4-Lyophilised wafer	 R5-Lyophilised wafer

- Hardness — 42 N, completely demolded
- Morphology — Cylinder, 12.2 mm in diameter, 2 mm in height, 24.5 mg in weight, flat and smooth on the surface
- Dissolution time — 2 seconds
- Drug content — 11.21 mg per tablet (93.68% of recovery)

➢ Reservoir development

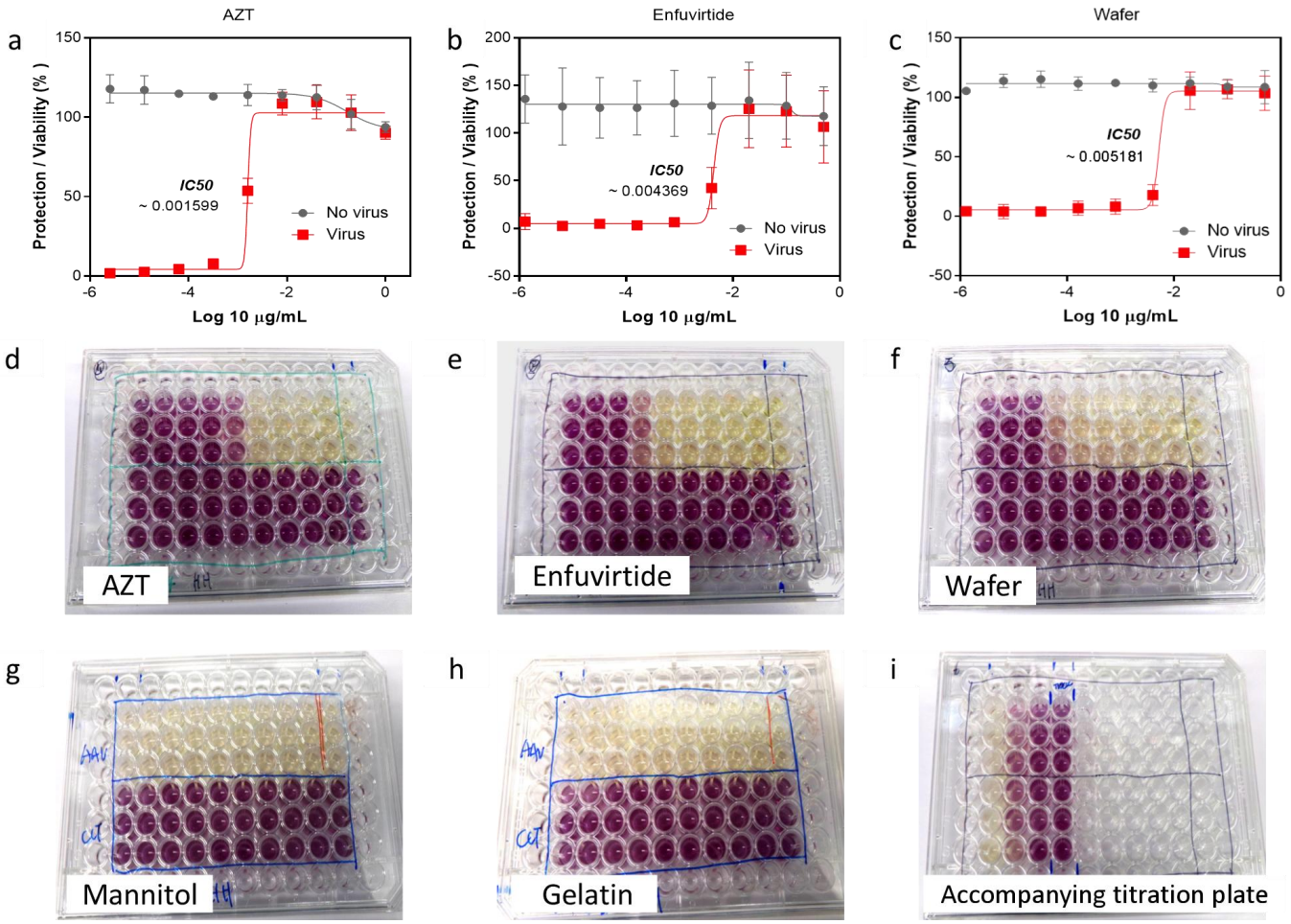


Figure 13. Antiviral activity and cytotoxicity of the reservoir.

Table 4. IC50 and CC50 of AZT, enfuvirtide, and enfuvirtide loaded into wafers and excipients against NL4-3 HIV-1-infected MT4 cells (n=3).

Compound	IC_{50} (ng/mL)	CC_{50} (µg/mL)
AZT	1.599	>1
enfuvirtide	4.369	>15
Wafer	5.181	>15
Mannitol	>15	>15
Gelatin	>15	>15

➢ *Ex vivo* study of HMAP associated with reservoir

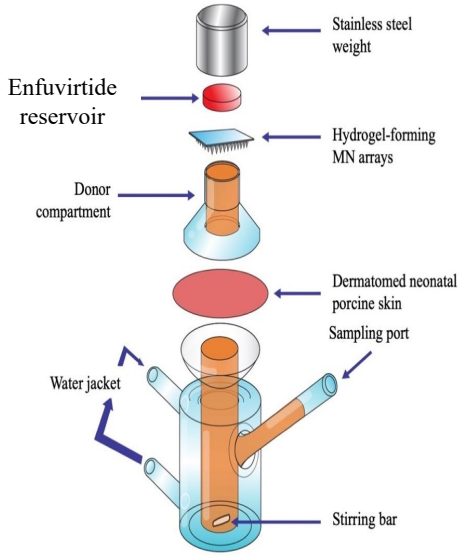


Figure 14. Franz cell system for *ex vivo* permeation studies.

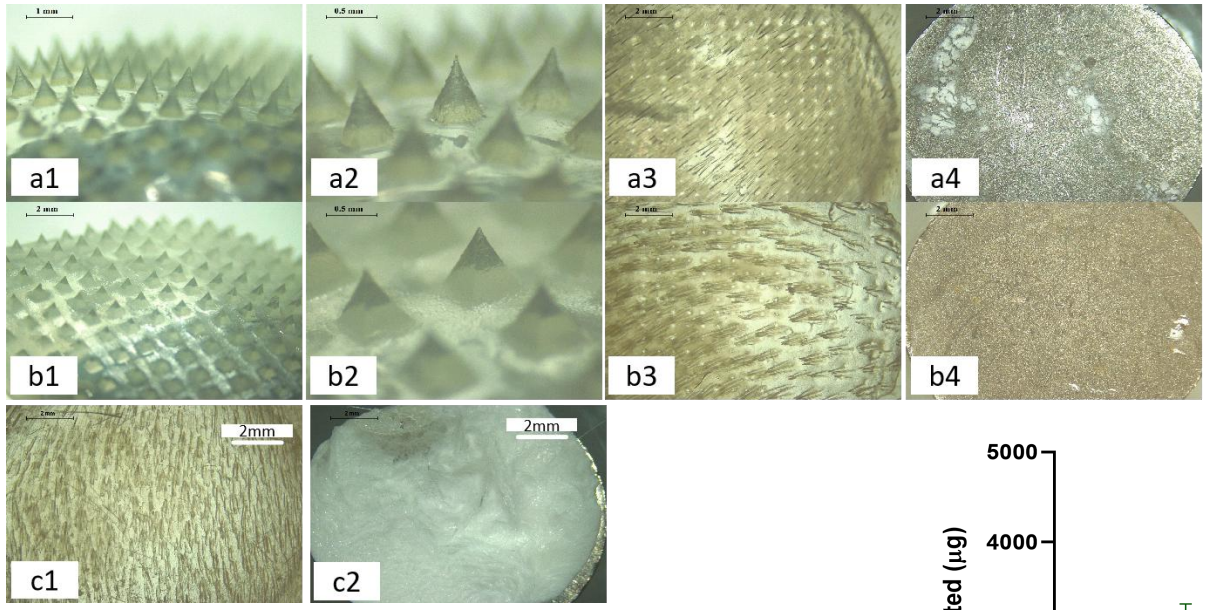


Figure 15. HMAP, skin and wafer after *ex vivo* study of 11*11 (a), 14*14 (b) HMAPs and control (c).

Table 5. Enfuvirtide permeation through pig skin from HMAPs in 24 h.

Geometry	Shape	24h permeation (µg)	24h permeation (%)
11*11	Conical	4006.34	36.26%
14*14	Pyramidal	3382.24	30.61%

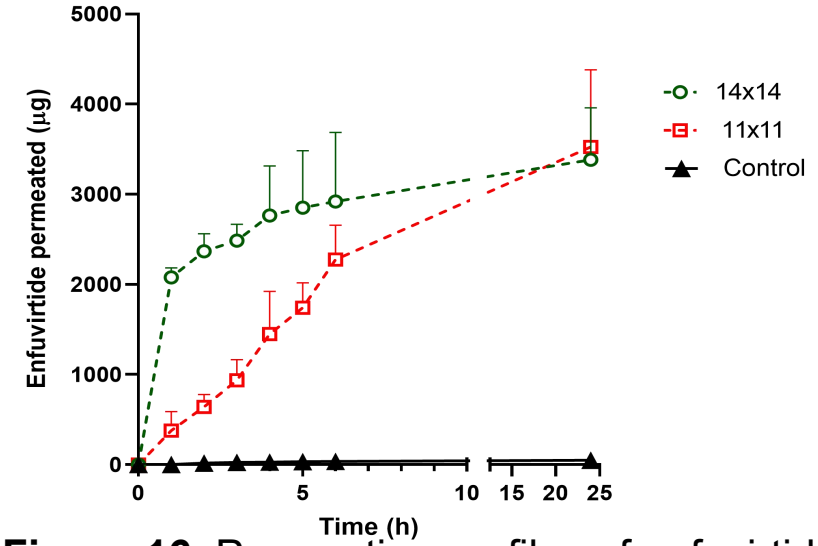


Figure 16. Permeation profiles of enfuvirtide in *ex vivo* study (Mean + SD, n=6).

Conclusions

- Combining quality by desgin and experimental design proves effective for optimising hydrogel formulation.
- HMAPs crafted from PVA/PVP/PEGdiacid with various geometries demonstrate potential for enhancing peptide delivery through skin.

Acknowledgements

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