Printing the Future of Vaccines: Dissolvable 3D printed microneedles using PbAEs for drug delivery

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Background

The deployment of vaccine programs, especially those utilising biologics like mRNA vaccines, can be hindered by the **cold chain dependency** of these biotherapeutics, **fear of needles**, **reliance on healthcare personnel** to administer injections, **sharps waste production**, and the **risk of counterfeiting**[1].

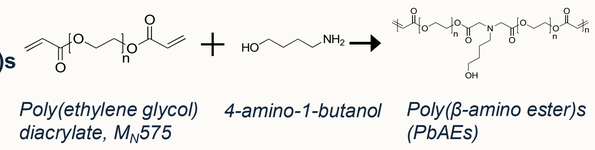
Dissolving Microneedle Patches (DMPs) can serve as a **potential vaccine delivery system**[2]**.** They consist of arrays of needles (<2000 µm) that can penetrate the stratum corneum and deliver therapeutic intradermally as they dissolve. Whilst the current fabrication method, **micromoulding**, is well established, it suffers from **restricted design flexibility** and **challenges with reproducibility**[2].

Light-based additive manufacturing technologies, such as stereolithography, provide an alternative route to **manufacturing DMPs**[3]. **Poly(β-amino esters) (PbAEs)** are particularly attractive materials for 3d printed DMPs due to their **printability, biodegradability** and ability to act as **gene-delivery vehicles**[4].

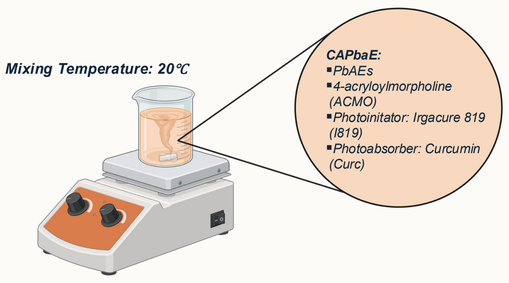
Methods

Resin Preparation

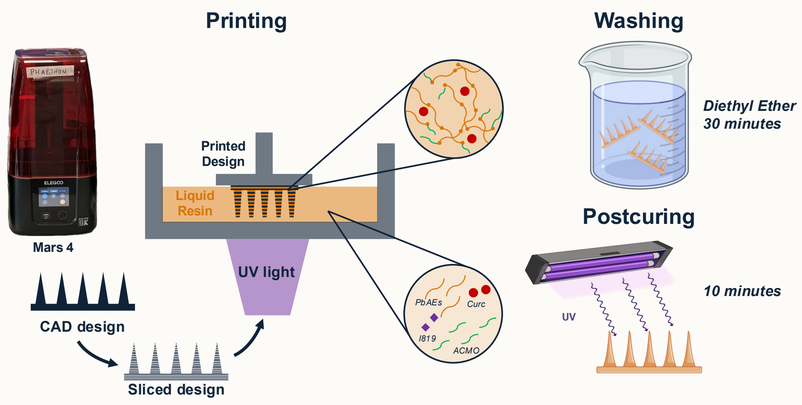
Poly(β-amino ester)s Synthesis



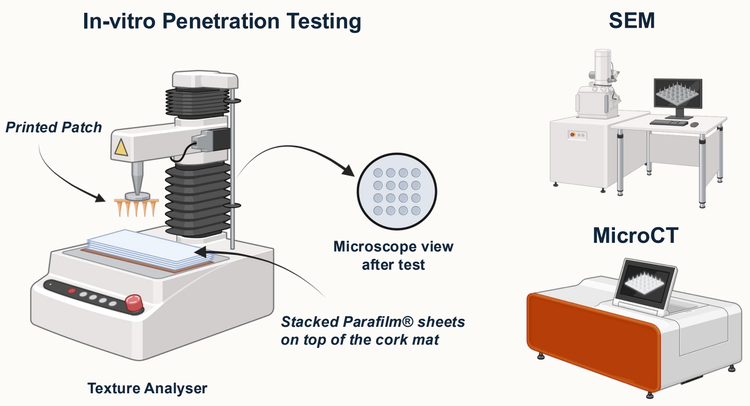
Resin Mixing



Microneedle Fabrication



Microneedle analysis



Results

Print Optimisation

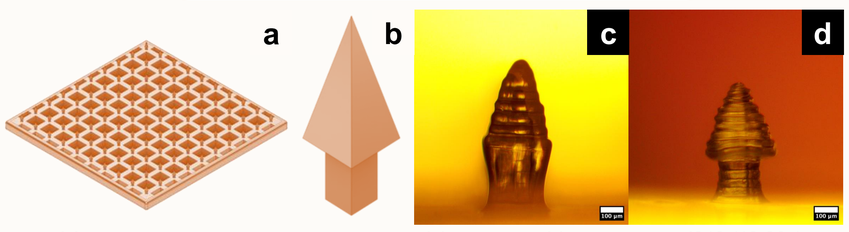


Fig. 1: (a) DMP CAD Design; *Arrowhead microneedle **(b)** CAD design **(c)** PbAEs: ACMO: I819 (19:80:1 wt%) **(d)** PbAEs: ACMO: Curcumin: I819 (18.9:80:0.1:1 wt%) post 30-minute Diethyl Ether wash (CAPbaE).*

- Grid-like design was employed for the patch base to **reduce the print warping**.
- **Arrowhead** needle design was selected to enable **detachment** of needle tips upon insertion.
- The PbAE:ACMO:I819 formulation (19:80:1 wt%) showed **good printability**.
- Feature sizes **down to 50 µm** were successfully printed, but prints showed **excess material** around the shaft due to overpolymerisation.
- Incorporation of **0.1 wt% Curcumin** and **30-minute** post-print wash in **diethyl ether** reduced the overpolymerisation, **improving the resolution to 20 µm** feature size.

In-vitro Penetration

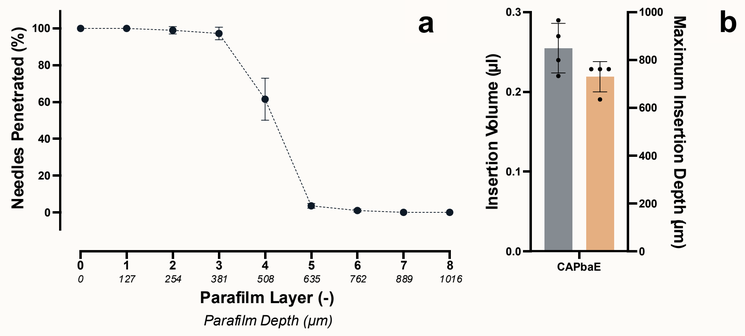


Fig. 2: ***(a)*** *Insertion profile of CAPbaE microneedle into Parafilm® layers **(b)** Insertion volume and maximum insertion depth of CAPbaE microneedles in Parafilm®.*

- Average depth of microneedle **penetration** was **460 ± 22 µm** (mean ± SD, n = 4) with **90% of needles** penetrating at least 381 µm of Parafilm® and **maximum insertion depth** was **730 ± 64 µm** (mean ± SD, n = 4)
- Average microneedle **insertion volume** was **0.27 ± 0.03 µl** (mean ± SD, n = 4) in Parafilm®.

Surface Topology

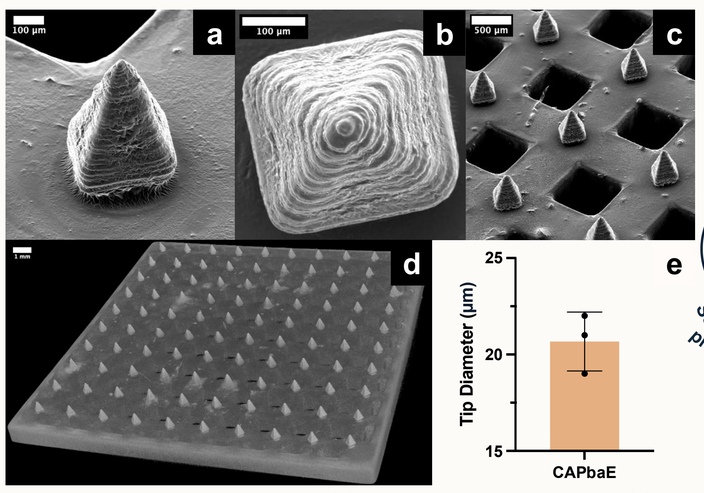


Fig. 3: SEM micrograph of CAPbaE DMP ***(a)*** *Single microneedle isometric view **(b)** Single microneedle top view **(c)** Patch isometric view; **(d)** MicroCT based 3D visualization of the DMP patch; **(e)** Tip diameter of CAPbaE arrowhead DMP.*

- Topology was investigated using SEM and MicroCT with samples showing **good printability** with minor defects and **average needle tip diameter** of **20 ± 2 µm** (mean ± SD, N=3, n = 5).

Print Dissolution

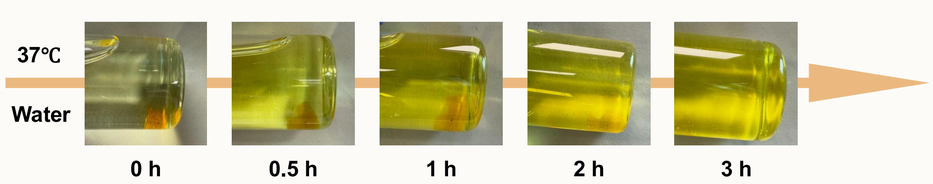


Fig. 4: *Timelapse dissolution of CAPbaE cube in deionised water at 37℃.*

- CAPbaE printed cube completely **dissolved** in **3 hours**.
- **100 needles** taken of the patch dissolved in **1 hour**.

Cargo Loading

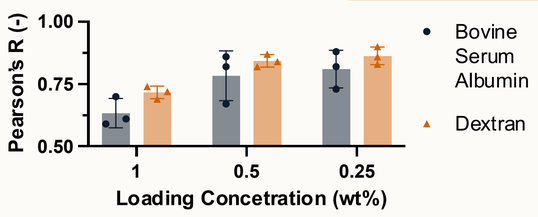


Fig. 5: *Printability of the bovine serum albumin and dextran loaded patches based on Pearson's R correlation of optical images of independent prints of loaded patches compared to the blank patches* (mean ± SD, n = 3).

- CAPbaE DMPs were loaded with **bovine serum albumin** and **dextran** and assessed in terms of **printability.**
- **Pearson's R correlation** was performed by comparing the optical images of **loaded DMPs** with the images of **blank DMPs**.
- **Print fidelity** was **maintained at low cargo loadings** but **decreased at higher concentrations** due to polymerisation around cargo particles.

Conclusions

- PbAE-based DMPs were successfully fabricated with feature sizes **down to 20 µm**.
- Fabricated DMPs exhibited **sharp tip geometries**, **effective penetration** into invitro skin model, and **dissolution capabilities** under aqueous conditions.
- Preliminary cargo loading data shows resin capability of printing loaded DMPs **without affecting print fidelity** at low loadings.

Future Work

- Assess the **material biocompatibility** of the printed DMPs.
- Investigate the **loading efficiency** of DMPs**.**
- Examine the **long-term thermal stability** of the DMPs.
- Optimize the **microneedle geometry** for improved skin penetration, dissolution.

Contact

References

[1] Forni, G., Mantovani, A., Forni, G. & Mantovani, A. COVID-19 vaccines: where we stand and challenges ahead. Cell Death & Differentiation 2021 28:2 28 (2021-01-21).
[2] Aldawood, F. K., Andar, A. & Desai, S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. Polymers 13 (2021-08-22).
[3] Ozyilmaz, E. D., Turan, A. & Comoglu, T. An overview on the advantages and limitations of 3D printing of microneedles. Pharmaceutical Development and Technology 26 (2021-10-21).
[4] Karlsson, J., Rhodes, K. R., Green, J. J. & Tzeng, S. Y. Poly(beta-amino ester)s as gene delivery vehicles: challenges and opportunities. Expert opinion on drug delivery 17 (2020-07-31).
[5] All images were created with BioRender.com unless specified otherwise.

Engineering and Physical Sciences Research Council EP/W017032/1