# Hydrogel-forming microarray patches with cyclodextrin drug reservoirs to enhance the long-acting delivery of the poorly soluble anti-HIV drug cabotegravir sodium

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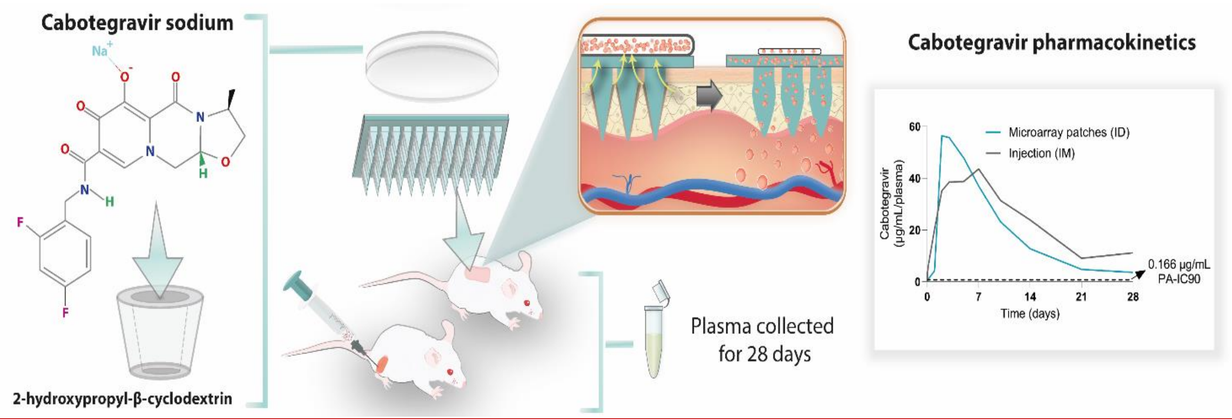
## INTRODUCTION

- Currently, HIV treatment takes the form of a daily drug regimen composed of multiple antiretroviral therapeutics, which, unfortunately is associated with a high pill burden and side effect incidence, leading to reduced patience adherence. Thus, there is an urgent need for alternative delivery systems that address these issues.
- Hydrogel-forming microarray patches (HF-MAPs) are one such alternative, offering minimally invasive and pain-free delivery of therapeutics over an extended period.
- Furthermore, these devices are designed to be self-administered by the patient and self-disabling meaning no contaminated sharps waste is generated from their use.
- Cabotegravir sodium (CAB-Na) is an anti-HIV drug for the treatment and pre-exposure prophylaxis of HIV infection [1].
- CAB-Na is also poorly soluble, which lends itself to depot formation following intradermal delivery.
- However, CAB presents significant challenges when the method of delivery is HFMAPs, which are inherently aqueous in nature.
- Herein, we have investigated the use of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) to improve CAB-Na aqueous-solubility and the effect this has on intradermal delivery via HFMAPs *ex vivo* and *in vivo*.




## METODOLOGY

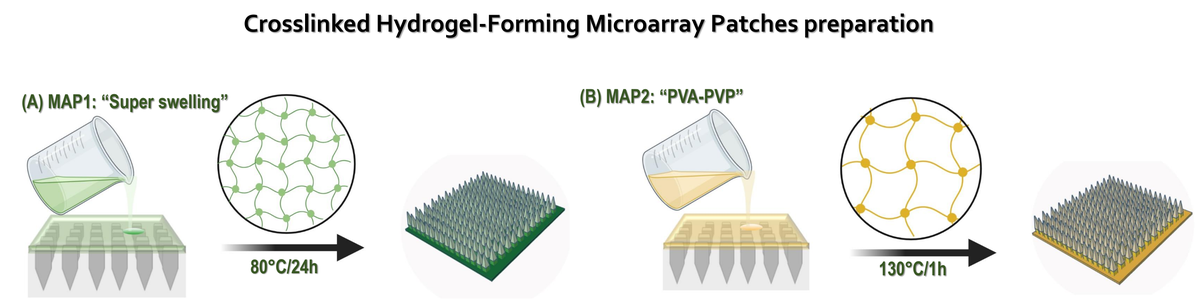



**Figure 1**: Two different HFMNs (0.5 cm2 array consist of 11x11 microneedles measuring 900 μm in height) were prepared from an aqueous blend (MAP1) of (A)"super-swelling" Gantrez-S97®:20%(w/w) Gantrez-S97®, 3%(w/w) Na2CO3 and 7.5%(w/w) PEG 10,000 with 24h of cross-linking/80°C and (MAP2) poly(vinylalcohol)-poly(vinylpyrrolidone) (B) (PVA-PVP): 25%(w/w) PVA 85- 120,000K, 4%(w/w) PVP 58,000K, 1.5%(w/w) citric acid, with 1h of cross-linking/130°C.

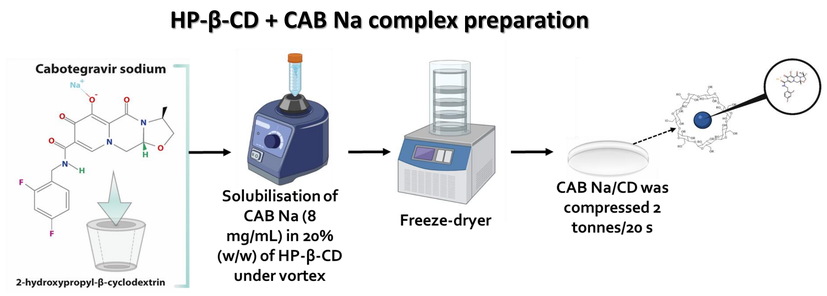



**Figure 2**: CAB-Na (8 mg/mL) was dissolved in an aqueous solution containing 20% (w/w) of HP-β-CD (Cavitron®W7/HP7) and then lyophilised. The dried CAB-Na/CD complex was compressed (2 tonnes for 20 s) to form a 250 mg tablet containing 8 mg of CAB Na.

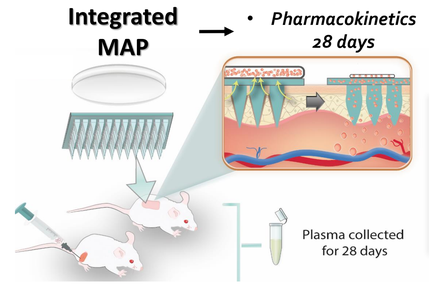



**Figure 3**: Integrated MAP was firstly tested using an *ex vivo* experiment using full-thickness skin. After selecting the ideal formulation, it proceeded to the *in vivo* pharmacokinetic studies over 28 days.

## RESULTS AND DISCUSSION

### Microarray characterisation

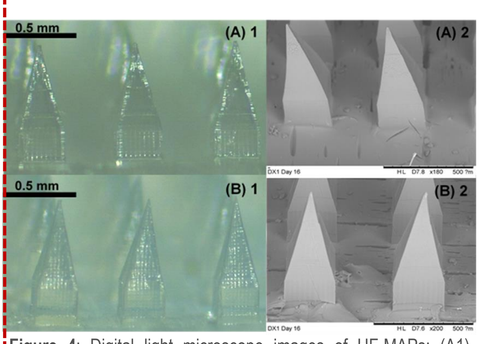



**Figure 4**: Digital light microscope images of HF-MAPs: (A1) MAP1 x35 and (B1) MAP2 x35 magnification. Scanning electron microscope images of HF-MAPs: (A2) MAP1 x180 and (B2) MAP2 x200.

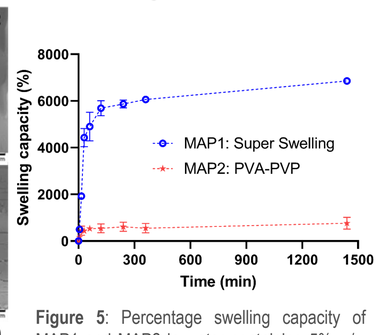



**Figure 5**: Percentage swelling capacity of MAP1 and MAP2 in water containing 5% w/w HP-β-CD (mean ± S.D., n = 3).

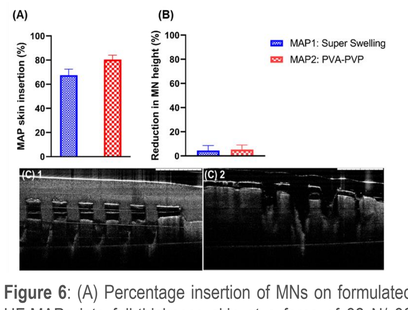



**Figure 6**: (A) Percentage insertion of MNs on formulated HF-MAPs into full-thickness skin at a force of 32 N/ 30 s/array (means ± SD., n = 5). (B) Reduction in MN height (%) noted following compression onto an aluminum block (32 N/ 30 s/ array) (means + S.D., n = 5). (C) Representative OCT images of HF-MAPs inserted in full-thickness neonatal porcine skin (C)1 = MAP1 and (C)2 = MAP2 (The scale bars represent a length of 1 mm).

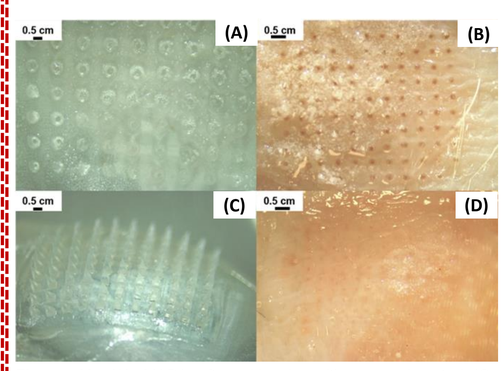
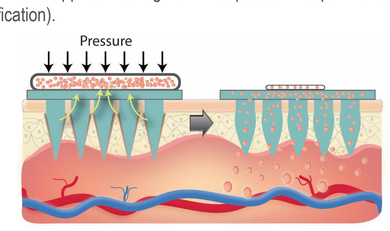



**Figure 11**: (A) MAP1 after skin deposition experiment (x12.5 magnification), (B) skin surface where MAP1 was applied during skin deposition experiment (x12.5 magnification), (C) MAP2 after skin deposition experiment (x8 magnification), and (D) skin surface where MAP2 was applied during skin deposition experiment (x12.5 magnification).




### *Ex vivo* release studies

**Table 2**: Mass transfer of CAB-Na from formulated tablets using MAP1, MAP2 and No MAP. The percentage values (%, w/w) were calculated in relation to 10.3mg of CAB-Na present in 250 mg CAB-Na/HP-β-CD tablet. (Means ± S.D., *n* = 6).

| Type of MAP | MAP1 -"Super-Swelling" | | MAP2 - PVA-PVP | | No MAP | |
|---|---|---|---|---|---|---|
| CAB-Na | μg | % | μg | % | μg | % |
| *Drug deposited skin/24h* | 141.63 ± 40.32 | 1.37 ± 0.50 | 324.00 ± 38.04 | 3.13 ± 0.43 | 21.13 ± 2.30 | 0.20 ± 0.02 |
| *Drug permeated/24h* | 67.27 ± 11.61 | 0.65 ± 0.02 | 132.60 ± 52.47 | 1.28 ± 0.22 | ND | ND |
| *Recovery MNs array* | 6650 ± 395.35 | 64.40 ± 4.99 | 4407 ± 650.62 | 42.68 ± 8.22 | * | * |
| *Recovery weight/donor compartment* | 273.20 ± 20.05 | 2.64 ± 0.28 | 4542 ± 1028.71 | 43.99 ± 12.99 | 6775 ± 5.68 | 65.16 ± 0.05 |
| *Recovery total* | 7132 ± 442.02 | 69.07 ± 5.59 | 9405 ± 588.74 | 91.08 ± 7.43 | 6796 ± 7.22 | 65.82 ± 0.06 |

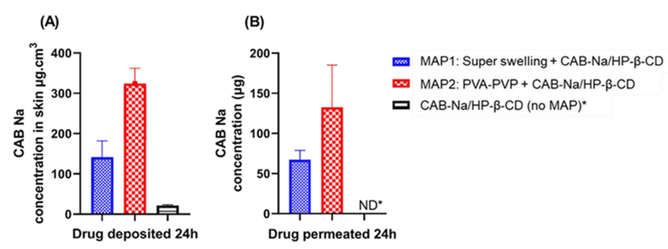



**Figure 12**: (A) Concentration of CAB-Na deposited into full-thickness skin after 24 h (B) Concentration of CAB-Na permeated through the skin after 24 h. (Means ± S.D., n = 6) ND* = drug was not detected

### HP-B-CD / CAB-Na complex characterisation

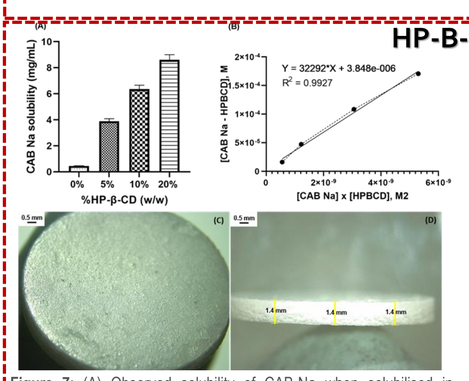



**Figure 7**: (A) Observed solubility of CAB-Na when solubilised in aqueous condition containing HP-β-CD at concentrations varying from 5 – 20% w/w (means + S.D., n = 12). (B) Solubilisation of CAB-Na in HP-β-CD solutions. Solubility of CAB-Na is linearly reliant on the concentration of HP-β-CD. The proportion found for the inclusion complex was 1:1 (CAB-Na: HP-β-CD) stoichiometrically. (C) Microscopic image of CAB-Na/HP-β-CD tablet upper surface and (D) Microscopic image of CAB-Na/HP-β-CD tablet lateral surface.

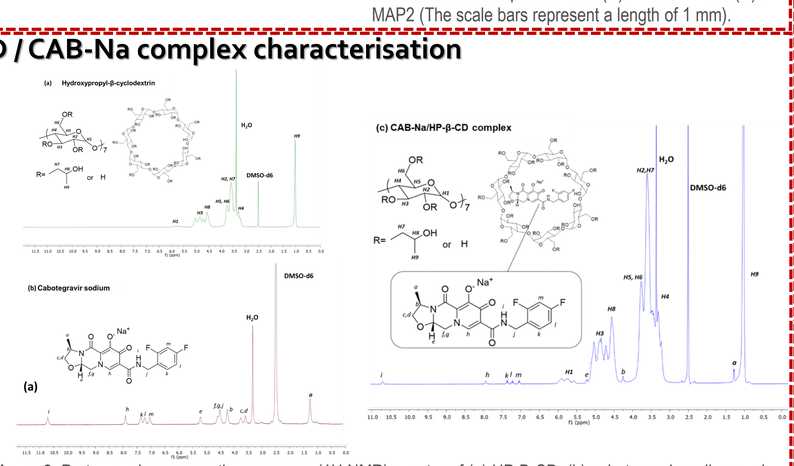



**Figure 8**: Proton nuclear magnetic resonance (1H NMR) spectra of (a) HP-B-CD; (b) cabotegravir sodium and (c) CAB-Na/HP-B-CD.

**Table 1**: Amount of CAB-Na present in lyophilised CAB-Na/HP-β-CD inclusion complex powder (100 mg) and in formulated CAB-Na/HP-β-CD tablets (250 mg) (means ± S.D., *n*= 12).

| Formulation | mg | % (w/w) |
|---|---|---|
| CAB-Na in 100mg of CAB-Na/HP-β-CD | 4.13 ± 0.02 | 4.13 ± 0.02 |
| CAB-Na (Tablet 250mg) | 10.32 ± 0.03 | 4.22 ± 0.03 |

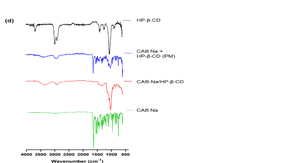



**Figure.9** FTIR spectra of CAB-Na, CAB-Na/HP-β-CD Complex, a physical mixture of CAB-Na and HP-β-CD (CAB-Na + HP-β-CD PM) and HP-β-CD.

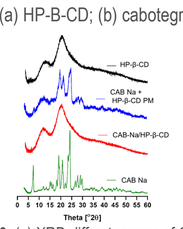



**Figure 10**: (a) XRD diffractograms of CAB-Na, HP-β-CD, a physical mixture of CAB-Na and HP-β-CD (CAB-Na + HP-β-CD PM), and CAB-Na/HP-β-CD inclusion complexes.

### *In vivo* studies

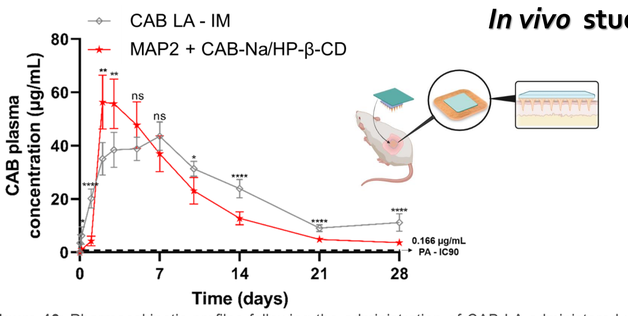



**Figure 13**: Pharmacokinetic profiles following the administration of CAB-LA administered via IM injection and CAB-Na delivered via MAPs (MAP2 + CAB-Na/HP-β-CD) (Means ± S.D., n = 6). Statistical analysis using an unpaired t-test was used to compare groups at each time point. Accordingly, ns denoted no significant difference (p > 0.05), * denoted p ≤ 0.05; ** denoted p ≤ 0.01 and **** denoted p ≤ 0.0001).

**Table 3**: CAB pharmacokinetic parameters in animals and their corresponding dose based on the body weight-normalised, following administration of CAB-Na delivered via MAPs (MAP2 formulation) and CAB-LA administered via IM injection (Means ± S.D., n = 6).

| Pharmacokinetic Parameters | CAB LA (IM) | CAB-Na (MAP2+ CAB-Na/HP-β-CD tablet) |
|---|---|---|
| *Applied dose (mg/rat)* | 2.5 | 40 |
| *Applied dose(mg/kg)* | 11.8 ± 0.5 | 189.4 ± 9.7 |
| $C_{max}$ *(μg/mL)* | 43.76 ± 5.36 | 58.98 ± 9.95 |
| $T_{max}$ *(day)* | 5.83 ± 2.05 | 2.83 ± 1.17 |
| $C_{28\ days}$ *(μg/mL)* | 11.2 ± 3.3 | 3.6 ± 0.8 |
| $AUC_{0\text{-}28}$ *(μg/mL*day)* | 644.76 ± 55.43 | 529.59 ± 86.42 |
| $AUC_{0\text{-}inf}$ | 816.48 ± 106.83 | 559.94 ± 92.44 |
| *MRT (day)* | 17.27 ± 4.09 | 9.71 ± 0.48 |
| $T_{1/2}$ *(day)* | 10.12 ± 2.73 | 5.79 ± 0.20 |
| *FR** | 1.00 | 0.049 ± 0.008 |

- 19-fold improvement in the aqueous solubility of CAB-Na was observed when in the presence of HP-β-CD (Figure 7);
- **XRD**: revealed a disappearance of the intense crystalline peaks observed during analysis of the pure drug. This finding indicated the conversion of the crystalline structure of CAB-Na to one that was amorphous, most likely due to successful CD/drug inclusion complex formation [2].
- **NMR**: some degree of Δδ (proton chemical shift) had occurred for H-3 and H-5. By monitoring the degree Δδ between H-3 and H-5, it can be confirmed that there was partial or complete drug inclusion into the CD [2].
- **FTIR**: The interaction between CAB-Na and HP-β-CD to form the complex of inclusion occurred in the H subjacent (CAB-Na) to the OH (HP-β-CD), clearly represented at 3363 cm-1 band and confirmed at the 1371 cm-1 stretching, suggesting a hydrogen bond interaction between CAB-Na and HP-β-CD occurred [2].
- *Ex vivo* skin deposition results for MAP1 and MAP2 showed that, per array, after 24 h, 141 ± 40 μg and 342 ± 34 μg of CAB-Na had been deposited into excised neonatal porcine skin, respectively (Figure 12).
- Based on these findings, MAP2 was taken forward for in vivo pharmacokinetic investigation, which was carried out over 28 days using rats. Following patch application, MAP2 demonstrated an extended drug release profile and an observed Cmax of 53.4 ± 10.16 μg/mL (Figure 13). This was superior to that of the FDA approved CAB nanosuspension (CAB-LA) which had a Cmax of 43.6 ± 5.3 μg/mL following intramuscular administration.

## CONCLUSION

- This work describes, for the first time, the successful delivery of a poorly soluble anti-HIV drug using HF-MAPs.
- The utilisation of effective CD complexation teamed with the rate-controlled delivery of high drug loads provided by the HF-MAP platform facilitated the delivery of clinically relevant doses of CAB-Na in an in vivo setting over a 28-day period following a single administration.
- The long-acting release was achieved by forming intradermal micro-depots in the skin using HF-MAPs.
- MAPs represent a promising alternative to the currently available oral and injectable treatments due to their ability to deliver HIV therapeutics at clinically relevant levels in a long-acting and minimally-invasive manner, without generating infectious sharps waste.
- The findings within demonstrate that the current delivery profile of the formulated MAP device is similar to that of an FDA-approved therapeutic marketed for PrEP and HIV treatment.
- Alternative delivery systems such as HF-MAPs have the potential to unlock benefits for those who are affected by HIV infection.

## AKNOWLEDGMENTS

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