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Strategies to reduce the wearing time of cabotegravir sodium dissolving microarray patches by facilitating fast tip detachment from baseplate

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SUMMARY

Dissolving microarray patches (DMAP) contain micron-scale projections and are usually made from biocompatible water-soluble polymers containing a high amount of drug in their tips, to be delivered through the skin layers. The challenge regarding DMAP is the detachment of the tips from the baseplate. This impacts the wearing time, the delivery efficiency into the skin, and patient compliance. In our previous work, we reported the delivery of cabotegravir sodium (CAB Na), an anti-HIV drug, necessitating a wearing time of more than 1 hour [1]. Herein were developed strategies to reduce the wearing time of DMAP containing cabotegravir sodium from hours to 10 minutes by facilitating tip detachment from the baseplate.

INTRODUCTION

Dissolving microarray patches (DMAPs) are one of the most promising types of polymeric microneedles (MAP). MAP has the advantage of allowing the release of any type of drug through the skin layers without pain or bleeding. They are made from hydrophilic and biocompatible polymers, which dissolve slowly, releasing the drug in a controlled manner. However, the big challenge is to implant the DMAP tips into the skin using hydrophilic tips. Usually, the baseplate requires a longer wearing time (from 1 to 24 hours) to completely detach the dissolving tips from the baseplate. Some approaches have already been described for hydrophobic tips such as poly(lactic-co-glycolic acid) or poly(caprolactone)[2]. However, for hydrophilic polymers, effective strategies have not been reported yet. In this work, were prepared eight different types of baseplates, aiming to facilitate tip detachment, improve the drug depositon in the skin, increase drug delivery efficiency and reduce wearing time from hours to less than 15 minutes.

MATERIALS AND METHODS

Materials: Poly (vinyl alcohol) (PVA) molecular weight (m/w) of 85-120 kDa, 87%–89% hydrolysed, poly (ethyleneglycol) (PEG) 10,000, Na2CO3 (sodium carbonate), acetonitrile (ACN) (HPLC grade), trifluoracetic acid, citric acid, and phosphate-buffered saline (PBS, pH 7.4) tablets were purchased from Sigma-Aldrich® (Dorset, U.K). Poly (lactic acid) (PLA) was obtained from Ultimaker® (Geldermalsen, Netherlands. Gantrez® S-97 (copolymer of methylvinylether and maleic acid 1500 kDa (m/w)), poly(vinylpyrrolidone) (PVP) K29-32 (58 kDa m/w). All other materials and chemicals were of analytical reagent grade.

Drug-loaded tips preparation*:* The first layer (drug tips layer) was prepared using an aqueous dispersion of CAB Na (27.63% w/w), PVA 10K (6.77% w/w), and PVP K32 (6.77% w/w). The first layer was cast using 16x16 molds, (cuboidal base (300 µm) / pyramidal tips (600 µm) containing a total of 900 µm height, 300 µm of base width / side, and 100 µm of interspacing) and submitted to a pressure chamber for 3 min/5 bar.

Baseplate preparation: Baseplates were prepared using the formulations described in **Table 1**.

MAPs preparation: All MAPs were prepared using the same first drug layer. Then, the 2nd or 3rd layers

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(baseplate) were cast according to each formulation described in Table 1. The baseplate is used to connect with the MAP tips and provide support to it when applied to the skin.

Wearing time and skin deposition: After preparing the CAB Na DMAPs with different baseplates, all of them were submitted to the wearing time study, where the MAPs were applied to the full-thickness pig skin (obtained from stillborn piglets) [1] for 10 minutes. After that, the MAPs were removed from the skin, and analysed using an optical microscope. The drug content deposited in the skin was analysed using HPLC-UV [1].

Table 1. *Composition of different baseplate strategies tested to improve the wearing time of CAB Na dissolving MAPs.*

Base-plate code	2nd layer (%, w/w)	3rd layer (%, w/w)
B1	PVA 50K: PVP K32 (15: 20) Aqueous blend- RT	---
B2	PVA 10K: PVP K32 (20: 20) Aqueous blend - RT	PLA 100% (3D printed)
B3	PVA 10K: PVP K32 (13.3: 13.3) Aqueous blend - RT	---
B4	PVP K90: glycerol (15: 5) Aqueous blend -RT	---
B5	PCL 37 Kda (100%)	---
B6	Gantrez S-97: PEG 10 kDa (20: 7.5) Aqueous blend - 80°C 24h	---
B7	Citric acid: sodium bicarbonate (1: 5) *Ethanol - RT	PVA 10K: PVP K32* Ethanol (13.3: 13.3)
B8	PVP K90 200µL (30) Aqueous blend -RT	---

*Dissolved in Ethanol; RT = dried at room temperature for 48h + 24h in the oven at 37°C.

RESULTS AND DISCUSSION

This work aimed to improve the wearing time of DMAPs described previously [1]. In that work, we were able to deliver 413 µg/CAB Na/MAP (0.5 cm²) in 24 hours. Aiming to reduce the wearing time down to 10 minutes, we tested the same baseplate (B1, Table 1). However, we were able to deliver only 230 µg/MAP (0.5 cm²) in 10 minutes. Among the tested formulations, the highest rate of drug deposition in the skin in 10 min was achieved by using the formulation n. 6, which is composed of a cross-linked hydrogel-forming attached to the MAP. Formulation n. 6 was able to deliver 400µg/CAB Na/ 0.5 cm² in 10 min, delivering statistically the same amount of drug as the 24 hours release from our previous work [1]. The hydrophilic nature of the crosslinked hydrogel (n. B6) interacts less with the hydrophobic formulation, tending to easily detach the tips into the skin, which explains the higher drug deposition when compared with other formulations tested (**Fig.1).**

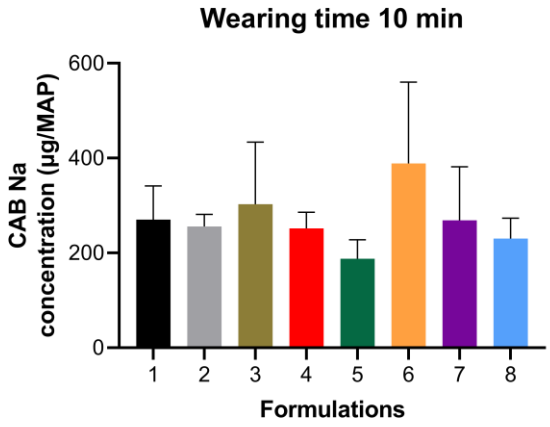

Fig. 1. *Graph presenting the drug deposited in the skin (ug/0.5 cm² DMAP) classified according to the different baseplate formulations. Data are reported as mean + SD (n = 6).*

CONCLUSIONS

The baseplate of formulation (n. B6) composed of a crosslinked hydrogel-forming presented the best skin deposition in 10 min, which reduced the wearing time from hours to 10 minutes. Using this strategy, we were able to deposit the same amount of CAB Na in 10 minutes only. This reduced wearing time will allow delivery of the drug intradermally in a short duration of DMAP application to the patient, consequently improving the patient adherence to the treatment.

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REFERENCES

I.A. Tekko,et al, Novel Bilayer Microarray Patch-Assisted Long-Acting Micro-Depot Cabotegravir Intradermal Delivery for HIV Pre-Exposure Prophylaxis, Adv. Funct. Mater. (2021) 2106999 https://doi.org/10.1002/adfm.202106999

W. Li, J. Tang, R.N. Terry, S. Li, A. Brunie, R.L. Callahan, R.K. Noel, C.A. Rodríguez, S.P. Schwendeman, M.R. Prausnitz, Long-acting reversible contraception by effervescent microneedle patch, Sci. Adv. 5 (2019) https://doi.org/10.1126/sciadv.aaw8145