DISSOLVING MICROARRAY PATCH-MEDIATED INTRADERMAL DELIVERY OF LONG-ACTING ANTIRETROVIRAL NANOSUSPENSIONS

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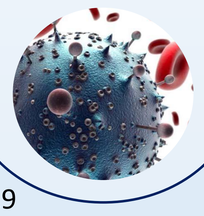
INTRODUCTION



Despite the recent widespread scale-up of antiretroviral (ARV) treatment and preventative measures, HIV remains a global epidemic, with approximately 37.9 million people affected worldwide, progressing at a rate of 1.7 million new cases per annum in 2018 (1). Sub-optimal adherence to oral multi-drug treatment regimens has emerged as the primary cause of therapeutic failure and development of drug-resistant virus (2).

Two long-acting (LA) injectable ARV nanosuspensions of rilpivirine (RPV) and cabotegravir (CAB) have entered clinical development, which may offer the potential to improve adherence in some patients by avoiding the need for lifelong daily oral dosing (3). However, administration *via* hypodermic needle and syringe presents significant barriers for the proposed therapy, particularly within low-resource settings (4). Transdermal delivery of such formulations presents as an attractive alternative, but only few drug compounds possess the required physicochemical characteristics to traverse the human skin barrier unaided. Microarray patches (MAPs) are micron-scale devices, which painlessly bypass the outermost layer of the skin, the *stratum corneum* (*SC*), by creating aqueous channels to facilitate transdermal and intradermal drug delivery (5).

Thus, utilising a combined dual-delivery approach, incorporating ARV nanosuspensions within dissolving MAPs, may permit effective intradermal administration, overcoming previous limitations associated with poor penetration across the *SC*. As such, MAPs may be viewed simply as a tool to deposit the "true" delivery system, the drug nanosuspension in the viable skin layers in sufficient amounts to afford sustained administration, thus avoiding issues with adherence to daily oral ARV treatment (6).

METHODS

1. Nanosuspension formulation

Novel RPV nanosuspensions were prepared through nanoprecipitation-ultrasonicaiton and, subsequently lyophilised. CAB LA nanosuspensions provided by ViiV Healthcare Ltd. were subjected to post-production processing to enhance concentration by removal of excess supernatant *via* needle and syringe.

2. Fabrication of dissolving MAP containing LA ARV nanosuspensions

Dissolving ARV MAPs were prepared by a simple micromoulding process (Figure 1) (7). Aqueous blends of polymer were mixed with lyophilised RPV or concentration-enhanced CAB LA nanosuspension, respectively. The blend was then spun at 5000 rpm for 1 min. The resulting formulations were then poured onto MAP moulds (19x19 array, 500 µm height, 300 µm base width), and a preformed polymeric baseplate positioned on top, proceeded by application of positive pressure (50 Psi) for 15 min to fill the mould microprojections. MAPs were then allowed to air dry for 24 h at room temperature. Final optimised RPV and CAB MAPs resulted in successful formation of MAPs, producing sharp strong tips with homogeneity across the arrays and, contained 1.7 mg and 2.8 mg of RPV and CAB, respectively. Optimised ARV MAPs are displayed in Figure 2.

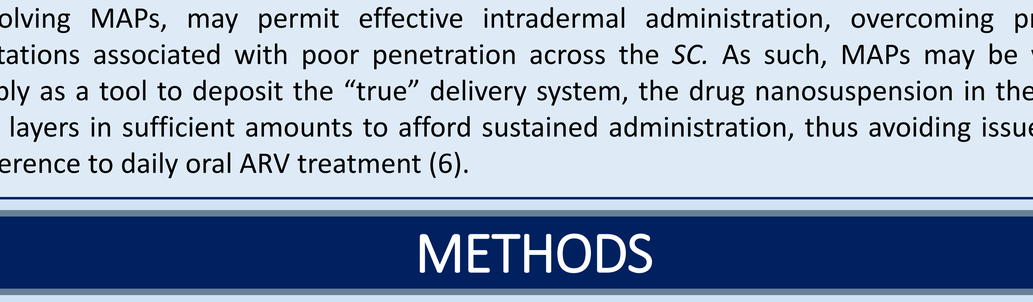


Figure 1. *Schematic representation of dissolving ARV MAP manufacture*

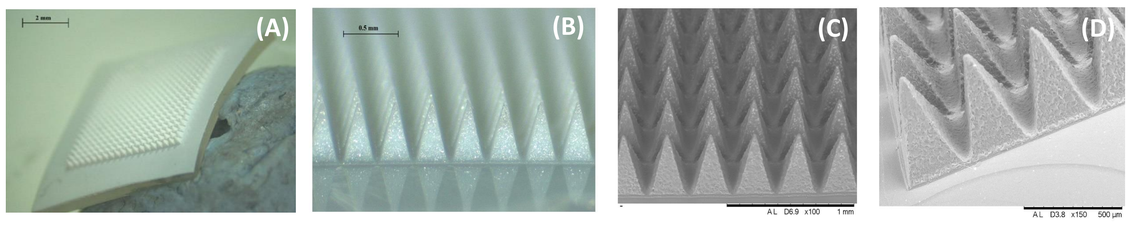


Figure 2. *Light microscope (A,B) and scanning electron microscope (C,D) images of ARV MAPs.*

3. *In vivo* delivery of ARV nanosuspensions from MAPs

Ethical permission for all *in vivo* experiments was obtained from the BSU at QUB. Two cohorts were employed in the *in vivo* studies: an experimental MAP cohort and an IM control cohort. Experiments were conducted using female Sprague Dawley rats aged 10 weeks. Prior to experimentation, rats acclimatised to laboratory conditions for a 7-day period. Four MAPs, two of each ARV, were applied to the back of shaved rats (1.7 mg RPV per MAP, 2.8 mg CAB per MAP), secured by breathable spandex for the rats comfort and, to keep the MAPs in place, which were then removed after 24 h (Figure 3). Those in the IM cohort received 10 mg/kg of RPV LA (2.5 mg dose) and 5 mg/kg CAB LA (1.25 mg dose) into the right and left hind thigh muscles, respectively. Plasma pharmacokinetic profiles were then followed over the next 12 weeks.

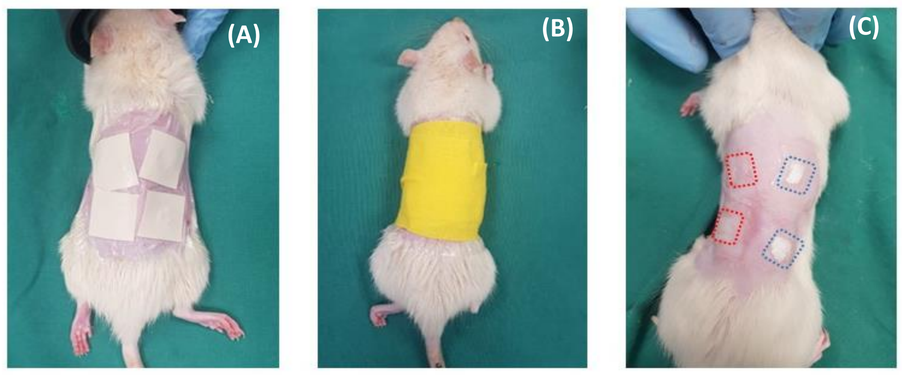


Figure 3. *Rats following application of four MAPs, secured with adhesive foam border and Tegaderm™ film (A), and wrapped in breathable spandex (B). Site of application post MAP removal (C) with visible implantation of MAP tips in skin (RPV highlighted by blue dashed square, and CAB by red dashed square in all cases).*

RESULTS & DISCUSSION

Quantification of RPV and CAB in rat plasma

Quantification of RPV and CAB in rat plasma was performed simultaneously using a RP-HPLC, partnered to a mass spectrometer, Agilent 1260® Infinity II series system. The column utilised for separation was an Inertsil ODS-3 5 µm (250 x 4.60 mm), and detection was conducted in ESI positive ion mode at m/z ratios of 367.4 and 406.3 for RPV and CAB, respectively.

ARV MAPs applied to the back of the rats in the treatment cohort were removed after 24 h, and in all cases dissolution of the MAP was achieved, despite a high content of hydrophobic drug particles. Therapeutically relevant concentrations of RPV and CAB, above the corresponding IC90 (12 ng/mL) or 4IC90 (664 ng/mL), were observed in the MAP treatment cohort following 1 h and 1-day sampling, respectively. Interestingly, mean plasma concentrations in the treatment cohort continued to rise following removal of the MAP for each ARV, as RPV displayed a C_{max} of 203 ± 183 ng/mL at a T_{max} of 2 days, and CAB displayed a C_{max} of 12,800 ± 5200 ng/mL at a T_{max} of 9 days, respectively. Therapeutically relevant mean plasma levels were still detectable to 63 and 28 days for RPV and CAB, respectively, as plasma levels fell below the corresponding inhibitory concentration at following time point (Figure 4).

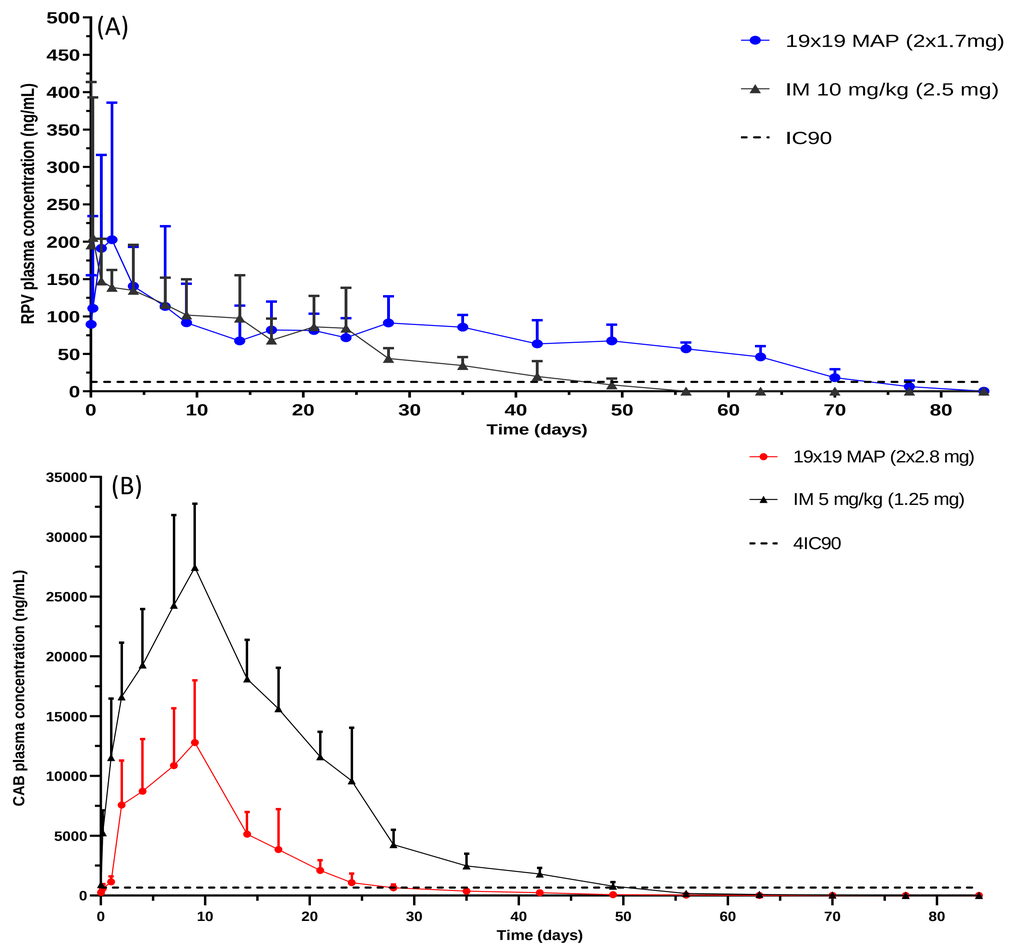


Figure 4. *Plasma pharmacokinetic profiles of RPV (A) and CAB (B) in rats following MAP or IM administration.*

This sustained release profile indicates that drug is still being released from micro-depots of drug nanocrystals as a result of intradermal deposition, further prolonged in the systemic circulation, while concurrently being cleared from the body. In support of this theory, implanted drug micro-depots were still visible in rats' back skin two weeks following MAP removal, indicating drug was still being released from this site (Figure 5).

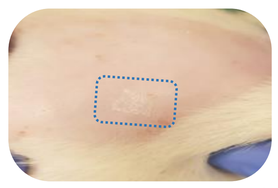
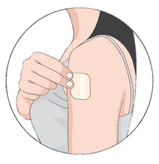


Figure 5. *Visible micro-depot of drug in the skin of rats' back*



Cautious extrapolation of the *in vivo* data obtained in rats to humans, loosely equates to a weekly patch size of 33.52 cm^2 and 125.42 cm^2 for RPV and CAB, respectively, required to maintain therapeutically relevant plasma concentrations.

CONCLUSIONS

This work documents a proof-of-concept study outlining formulation of a dual-delivery approach, combining novel LA ARV nanosuspensions within dissolving MAP systems for intradermal delivery to afford a sustained drug administration. This is the first time that an investigational ARV treatment regimen has been incorporated into a dissolving MAP delivery format, and illustrating the potential of the platform for two or more agents. Thus, future use of MAPs in the needle-free delivery of ARVs for the prevention and treatment of HIV infection deserves exploration. Formulation optimisation, comprehensive preclinical pharmacokinetic evaluation, biodistribution, physiologically-based pharmacokinetic modelling and patient acceptability studies are now necessary to fully realise the potential of these novel delivery platforms.

ACKNOLEDGEMENTS

The authors would like to acknowledge both Janssen Pharmaceutica and ViiV Healthcare Ltd. for their support, and provision of active pharmaceutical preparations.

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