

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

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**Background:** Despite the recent up-scaled use of antiretroviral (ARV) treatment and preventative measures, HIV remains a global pandemic, affecting approximately 37.9 million people worldwide in 2018. Sub-optimal adherence to oral multi-drug regimens has emerged as the primary cause of therapeutic failure and development of drug-resistant virus. Accordingly, there is an urgent need for the development of self-administered long-acting (LA) delivery methods to overcome existing issues with daily oral adherence. Alternatives in clinical development include two LA intramuscular (IM) injectable ARV nanosuspensions of rilpivirine (RPV) and cabotegravir (CAB). However, their administration requires regular access to healthcare resources and sharps disposal facilities. As a result, this proof-of-concept study was designed to evaluate the potential intradermal delivery of LA RPV and CAB *via* dissolving microarray patches (MAPs). As such, MAPs are utilised simply as a tool to deposit the ARV nanosuspension within the viable skin layers in sufficient amounts to afford sustained administration, thus avoiding the need for adherence to daily oral treatment.

**Methods:** Dissolving ARV MAPs were prepared by a simple micromoulding process. Aqueous blends of polymer were mixed with lyophilized RPV LA or concentration-enhanced CAB LA nanosuspension, respectively. 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 the application of positive pressure. MAPs were then air dried for 24 h at room temperature, resulting in two MAP systems containing 1.73 mg RPV LA and 2.81 mg CAB LA, respectively. The backs of Sprague-Dawley rats were then shaved and in the treatment cohort 4 MAPs were applied (2 RPV and 2 CAB), and in the control cohort rats received 10 mg/kg of RPV LA IM and 5 mg/kg of CAB LA IM, respectively. Mean plasma concentrations of each ARV were simultaneously quantified by RP-HPLC-MS and pharmacokinetic profiles were established over the following 12 weeks.

**Results:** ARV MAPs applied to the back of the rats in the treatment cohort were removed after 24 h, and despite a high content of hydrophobic drug particles, complete MAP dissolution was achieved in all cases. Therapeutically relevant concentrations of RPV and CAB above the relevant IC<sub>90</sub> 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<sub>max</sub> of 203 ± 183 ng/mL at a T<sub>max</sub> of 2 days, and CAB displayed a C<sub>max</sub> of 12,800 ± 5200 ng/mL at a T<sub>max</sub> of 9 days, respectively. Therapeutically relevant mean plasma levels were still detectable to 70 and 28 days for RPV and CAB, respectively. This indicates that drug is still being released from intradermal micro-depots of solid-drug nanocrystals, further prolonged in the systemic circulation, while concurrently being cleared from the body.

**Conclusions:** This proof-of-concept work outlines the formulation of novel LA ARV nanosuspensions within dissolving MAP systems for intradermal delivery affording a sustained drug administration. This is the first time that an investigational ARV treatment regimen has been incorporated into a dissolving MAP format, and illustrates 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.