FORMULATION OF CATIONIC ANTIRETROVIRAL NANOCRYSTALS AND SUBSEQUENT INCORPORATION INTO A DISSOLVING MICRONEEDLE ARRAY

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Background: At the end of 2019, 38 million people were living with human immunodeficiency virus (HIV), which is recognised by the World Health Organization as a major global health problem. Of these 38 million cases, 1.7 million were new diagnoses, three times higher than the UNAIDS 2020 target. Current HIV treatments are usually delivered orally or *via* intramuscular injection. This project involves formulating nanosuspensions (NS's) of two antiretroviral drugs, cabotegravir (CAB) and rilpivirine (RIL), into separate dissolving microneedle (MN) arrays which when applied to the skin offer a patient-friendly alternative to hypodermic needles for long acting delivery.

Methods: To increase drug loading and increase the efficiency of drug delivery, both RIL and CAB were formulated into nanocrystals *via* wet bead milling on a small scale. 7 mL glass vials were used as a closed vessel with 0.1-0.2 mm yttria stabilised zirconium beads employed as the milling media. Energy was provided to the system with the use of a magnetic stir plate rotating at 1250 rpm alongside two 25x8 mm stir bars in the vessel. For the RIL NS, 444.2 mg of drug was placed in the vessel and the CAB NS was formulated with 400 mg of drug. In both cases the surfactant solution used to stabilise the system was 5 mL of a mixture of d-α-tocopheryl polyethylene glycol succinate 1000 (TPGS) 1.02% and chitosan medium viscosity 0.05% w/w. After 20 hours of milling the NS was recovered through a 200-mesh sieve. Particle analysis was conducted using a Brookhaven Nanobrook Omni. NS obtained were lyophilised to concentrate the drug and increase stability. This was done by freeze-drying the NS in a 1:1 weight ratio with a solution of poly (vinyl alcohol) (PVA) 9-10 kDa 2% and poly (vinyl pyrrolidone) (PVP) 58 kDa 2% w/w which was used as a cryoprotectant to preserve nanocrystal characteristics. MN arrays were formulated in a two-step process. 100 mg of lyophilised NS was combined with 200 µL of water in a SpeedMixer at 3000 rpm for 5 minutes. An excess of this formulation was spotted onto the centre of silicon MN moulds. Each mould contained 600 pyramidal needles with a height of 750 µm, base width of 300 µm and 50 µm needle interspacing at the base. These moulds were placed under positive pressure of 4.5 bar for a total of 10 minutes, after which the excess formulation was removed, and these were left to dry at room temperature for 20 hours. A second layer was then added as the baseplate, 300 mg of PVP 58 kDa 30% w/w, and centrifuged for 10 minutes at 3500 rpm then left to dry for 20 hours at room temperature. Following removal from the moulds, MN were characterised using a light microscope. Drug content analysis was performed using HPLC-UV analysis.

Results: Prior to lyophilisation, RIL NC had a particle size of 163.13 ± 5.46 nm and a PDI of 0.109 ± 0.006 (n = 3). Particle size was retained during lyophilisation and zeta potential was determined to be +16.87 ± 0.53 mV (n = 3). CAB NC had a particle size of 194.79 ± 2.70 nm and a PDI of 0.129 ± 0.037 (n = 3). Particle size was again retained during lyophilisation and zeta potential was +17.29 ± 0.26 mV (n = 3). Both sets of MN arrays were well formed and had good mechanical strength on insertion. Each RIL MN array was found to contain 2.47 ± 0.39 mg of drug while CAB MN contained 3.09 ± 0.15 mg (n = 3).

Conclusions: NS of RIL and of CAB were successfully formulated with the desired characteristics *via* wet bead milling. These NS were lyophilised and incorporated into dissolving MN arrays which were well formed, had good mechanical strength and high drug loading. Further studies are needed to assess the *in vitro* release and delivery of the drug from these MN arrays.