



Introduction

Human immunodeficiency virus (HIV) was first reported as a fatal disease of young gay men and intravenous drug users in 1981. The virus was identified in 1983. In the early years, many people died of causes related to HIV because of the lack of effective treatment options [1]. According to the World Health Organisation (WHO), HIV continues to be a major global public health issue, having claimed more than 32 million lives so far. Currently, approximately 38 million people are living with HIV, with 1.7 million people becoming newly infected each year. Even though HIV is a global disease, the most affected region is the African continent. Up-to-date, HIV infections are still not curable, however, developments in antiretroviral therapy control the virus effectively [2].

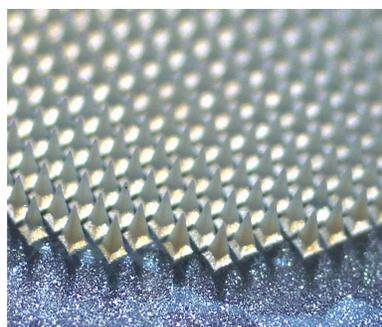


Figure 1. Bilayered microarray patch loaded with rilpivirine nanocrystals.

Antiretroviral agents, such as the non-nucleoside reverse transcriptase inhibitor rilpivirine (RIL), are commonly delivered orally or intramuscularly. However, a more patient friendly alternative drug delivery system is highly desirable, especially in low resource settings, to improve patient acceptance. Thus, dissolving bilayered polymeric microarray patches (MAPs) for the intradermal delivery of RIL were developed (Figure 1). To achieve high drug loading while maintaining mechanical stability of MAPs a nanosuspension of RIL was prepared by bead milling at laboratory scale prior to MAP fabrication. To allow for translation to industrial setting, the approach was designed in an easily up-scalable fashion.

Materials & Methods

The RIL nanosuspension was prepared in a top-down approach by small scale bead-milling in a glass vial (total volume 10 mL) using ceramic milling beads (12 g, 0.1-0.2 mm) and two magnetic stir bars (25 x 8 mm) to facilitate bead movement (Figure 2). RIL (0.25 g) and a surfactant solution (5.5 mL) containing 2% w/w poly(vinyl alcohol) 9-10 kDa and 2% w/w poly(vinyl pyrrolidone) 58 kDa were added to the vial and milled at 1,500 rpm at an angle of 75° for 24 h. After separation from ceramic milling beads, the nanosuspension was made up to a total volume of 6 mL and lyophilised. Particle sizes were measured using a NanoBrook Omni Particles size analyser and RIL content was analysed using a validated UV-HPLC method.

The lyophilised nanosuspension was reconstituted in 710 µL deionised water and the resulting hydrogel was immediately used for casting the first layer of MAPs (100 µL/MAP) into silicone micromoulds (600 pyramidal needles, height 750 µm, base 300 x 300 µm, interspacing 50 µm). Following pressure application (5 bar, 15 min), excess formulation was removed and MAPs were dried for 2 h at room temperature. To form a mechanically strong baseplate, 0.7 g of an aqueous poly(vinyl pyrrolidone) 360 kDa blend (30% w/w) was cast on top of the first layer, followed by centrifugation at 3,500 rpm for 15 min (Figure 2).

After further drying for 18 h, MAPs were demoulded and tested in terms of their mechanical strength (compression at 32 N against an aluminium surface using a Texture Analyser) and insertion efficiency into a previously validated skin model (Parafilm M®, 8 layers) [3]. Drug content was calculated based on the total needle volume of 13.5 mm³ and additionally measured by dissolving 10 individual needles (HPLC analysis).

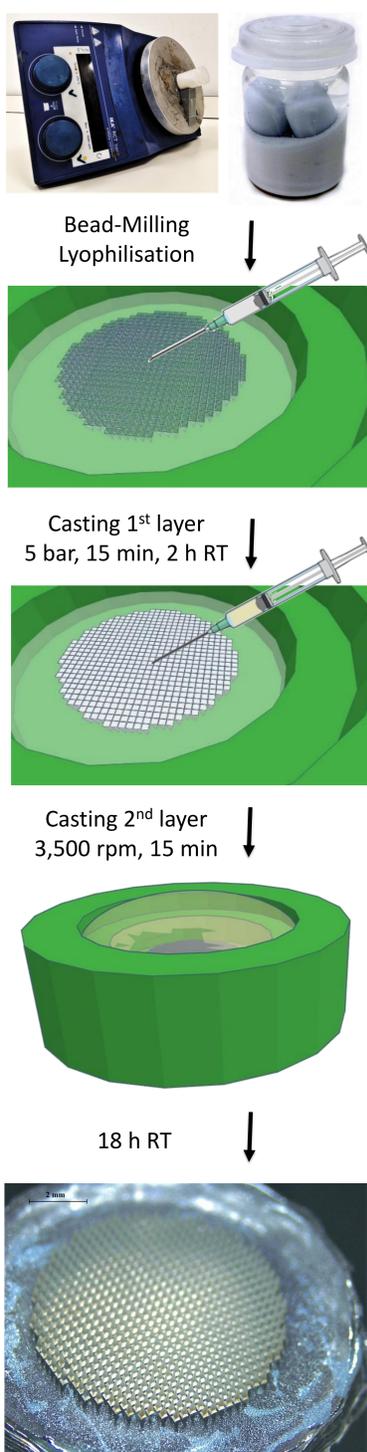


Figure 2. Fabrication process.

Results & Discussion

The nanosuspension had a mean particle size of 168 ± 2 nm (PDI 0.18 ± 0.02, n = 9) before and 169 ± 3 nm (PDI 0.20 ± 0.05, n = 9) after lyophilisation and reconstitution (Figure 3). The average drug content was 182 ± 19 mg (n = 3).

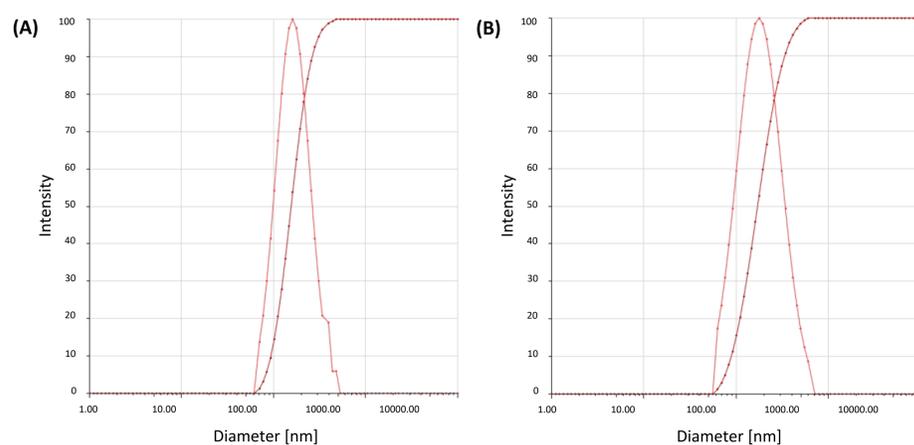


Figure 3. Particle size of rilpivirine nanocrystals (A) before and (B) after lyophilisation.

Observation of MAPs under a light microscope showed two clearly separated layers with RIL visible in the upper needle shafts only and a clear baseplate (Figure 1, 2). MAPs were compressed 9 ± 6% (n = 48, 16 needles on 3 different MAPs) of their total needle height of 750 µm. They inserted up to the third layer of Parafilm M® (Figure 4) which equals approximately 50.8% of the total needle height (n = 3).

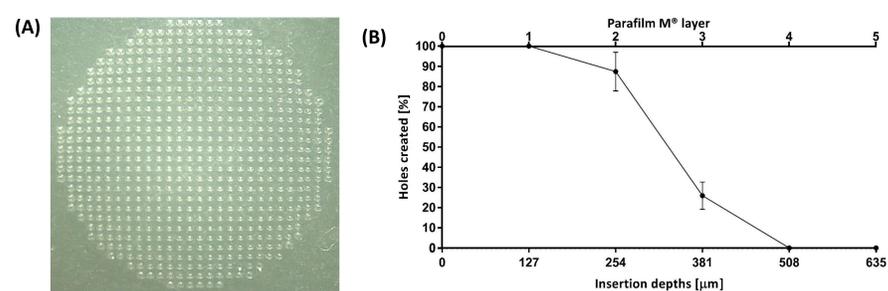


Figure 4. (A) Image of 1st layer of Parafilm M® after insertion and removal of microarray patches. (B) Percentage of holes created in each Parafilm M® layer.

Based on theoretical calculations, considering the measured drug content of the prepared nanosuspension, the total needle volume of 13.5 mm³ and the composition of the reconstituted lyophilisate (63% water, 16% RIL, 22% polymers), MAPs had a total drug load of 2.2 mg/ array. However, HPLC analysis of 10 individual needles revealed an extrapolated drug load of 2.5 ± 0.2 mg RIL/MAP (n = 9, 3 repeats per MAP, 3 different MAPs).

Conclusion

Dissolving RIL loaded MAPs had to clearly separated layers with the drug located in the needle shafts only. They were mechanically strong and could be easily inserted into a validated skin model regardless of their high needle density. Due to the formulation of RIL as a nanosuspension, a high drug load of approximately 2.5 mg was achieved. As the formulation process consisted only of a small number of steps and employed methods commonly used in industrial settings, such as bead milling, up-scaling is feasible. Further studies will need to be conducted to evaluate in skin dissolution times and drug deposition in *in vitro* and *in vivo* settings.

References

- [1] Wing EJ. 2016. HIV and aging. *Int. J. Infect. Dis.* 53, 61–68.
- [2] World Health Organisation. 2019. Fact sheet HIV/AIDS. Available from: <https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids>, [29/10/2019].
- [3] E. Larrañeta *et al.* 2014. A proposed model membrane and test method for microneedle insertion studies. *Int. J. Pharm.* 472, 65-73.