

Intradermal delivery of long-acting bictegrovir nanosuspension-loaded microneedles for potential treatment of HIV infection

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Background: HIV/AIDS affects approximately 36.7 million people worldwide. Oral administration is one of the commonly used options for HIV treatment. However, one drawback is poor patient compliance given the lifelong, daily dosing required. Transdermal delivery possesses advantages in maintaining stable drug plasma levels by eliminating the first pass effect, resulting in reducing daily dose requirement. Microneedles are transdermal drug delivery devices that painlessly by-pass the *stratum corneum*. The development of long-acting nanosuspension (NS) HIV drugs potentially promises to improve the adherence. Dissolving microneedles (DMNs) can deposit NS in the viable skin layers for absorption by the dermal microcirculation and also possibly uptake by the lymphatic system, an important reservoir for HIV virus. Accordingly, this study aimed to deliver BIC intradermally for sustained absorption.

Methods: BIC NS was manufactured by a wet media milling technique using 1% w/w PVA (10 kDa) and ceramic beads as milling media. The particle size and polydispersity (PDI) of NS was optimized by increasing milling time. Cryoprotectant of PVP (K29-32) was added in optimized NS, which were lyophilized in the freeze dryer for 25 h. Particle size and PDI were measured with dynamic light scattering (DLS). The NS was characterized based on attenuated total reflectance fourier transform infrared (ATR-FTIR). The first layer of DMNs (needle density of 16 × 16, 600 μm pyramidal needles with 250 μm column shaft, 300 μm width at base and 300 μm interspacing) were prepared from the aqueous blend of BIC NS by applying positive pressure in pressure chamber (5 bars, 2.5 min) and 30% w/w PVP (360 kDa) was used to cast the baseplates with the centrifugation (3500 rpm, 15 min). Mechanical study and Parafilm M[®] insertion were also carried out to characterize the DMNs.

Results: DLS reports of BIC NS confirmed that milling time was able to influence the particle size. The NS formulation prepared with a milling time of 24 hours exhibited the smallest particle size (396.11 ± 28.67 nm) and PDI (0.17 ± 0.04). The lyophilized NS gave good resuspension in deionized water after slightly shaking. The particle size and PDI of the NS obtained after lyophilization were 390.34 ± 37.65 nm and 0.192 ± 0.02, respectively. According to ATR-FTIR spectra, the major peaks retained in NS compared with pure drug powder and no additional peaks were observed, indicating that there were no chemical interactions between pure drug and excipients. Digital microscope images clearly showed the DMNs had sharp tips filled with BIC NS and transparent baseplate. The percentage of height reduction of DMNs was less than 10% and the insertion depth into Parafilm M[®], a skin simulant, was up to 504 μm.

Conclusions: The NS formulation and NS-loaded DMNs were successfully developed. In future studies, drug deposition, *ex vivo* dermatokinetic study, skin distribution, as well as *in vivo* pharmacokinetics will be explored.