Intradermal delivery of long-acting bictegravir 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.

Materials and methods

Fabrication and optimisization of bictegravir nanosuspensions

- Bictegravir (BIC) nanosuspension(NS) was produced using a wet media milling technique.
- Ceramic beads with the diameter of 0.1-0.2 mm and 1% w/w PVA (10 kDa) was used as milling media and polymeric stabilizer, respectively.
- The optimization of particle size was based on drug loading and milling time of the grinding process.
- Aliquots (70 mg) of PVP (K29-32) as a cryoprotectant, was added in optimized NS, which were lyophilized in the freeze dryer at – 40°C overnight.

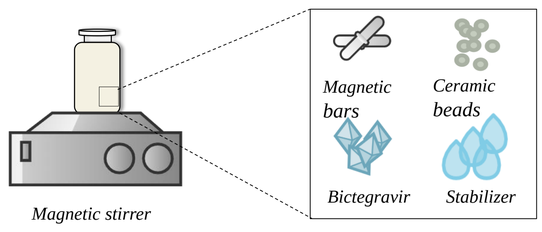

Figure 1. Schematic representation of fabrication of nanosuspensions

Characterisation of bictegravir nanosuspensions

- A NanoBrook Omni Particle size analyser was used for measuring the particle size and PDI of obtained nanosuspensions.
- Attenuated total reflectance fourier transform infrared (ATR-FTIR) was performed to identify the drug-excipients interaction according to the molecular vibration in the drug powder and NS formulation. The range of measurement was recorded from 4000 to 600 cm^{-1} and the resolution used in analysis procedure was 4 cm^{-1}.
- Differential scanning calorimetry (DSC) study of drug powder, lyophilized NS and physical mixture was carried out on a Q100 Differential Scanning Calorimeter.

Fabrication of nanosuspension-loaded microneedles

- The bictegravir NS-loaded MNs (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 in two steps.
- The first layer of MNs was prepared from the aqueous blend of BIC NS and the baseplate was fabricated with aqueous PVP (K 90) gel.

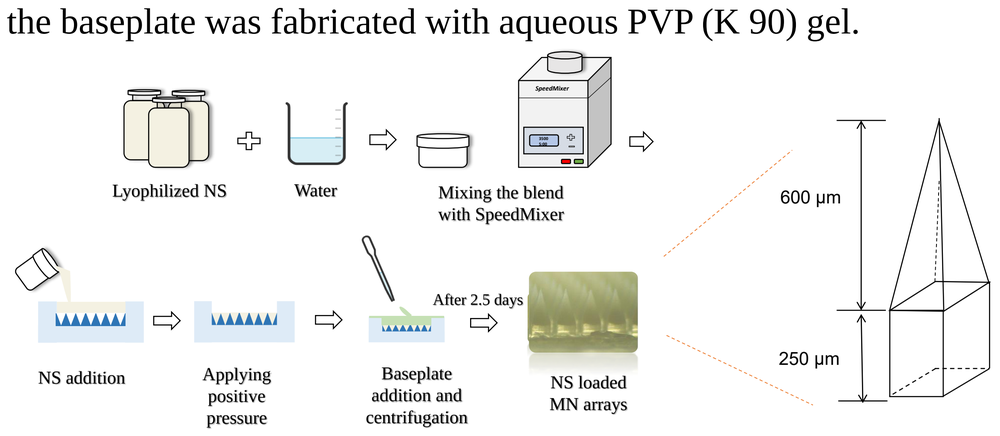

Figure 2. Schematic representation of fabrication of NS-loaded MN arrays.

Characterisation of nanosuspension-loaded microneedles

- Texture Analyser was applied to evaluate mechanical study and insertion behavior.
- Parafilm M® was regarded as a skin simulant for MN insertion. The Parafilm M® was folded into an eight-layer sheet (1 mm thickness). A force of 32 N was applied to MNs by Texture Analyser and held for 30s.
- The deposition of BIC from MNs was investigated to quantify the amount of drug in full-thickness neonatal porcine skin.

Results and discussion

- The optimized NS prepared with a milling time of 24 h exhibited the smallest particle size (396.11 ± 28.67 nm) and PDI (0.17 ± 0.04) ($P<0.05$) with the drug loading of 200 mg. (Figure A and B)
- The particle size and PDI of the NS obtained after lyophilization were 390.34 ± 37.65 nm and 0.192 ± 0.02, respectively. (Figure C)
- According to ATR-FTIR spectra, the major peaks retained in NS compared with pure drug powder and no additional peaks were observed, which explains that there were no chemical interactions between pure drug and excipients. (Figure D)
- The intense peak appeared in BIC and the physical mixture corresponded to the melting point of drug crystals (213°C), while the peak completely disappeared in NS, indicating the change of the nature of drug from crystalline to amorphous. (Figure E)

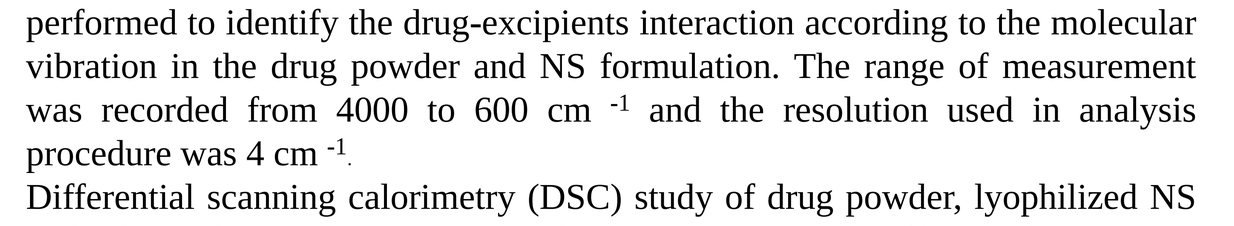

Figure 3. (A) Influence of milling time on the particle size and PDI (Means ± SD, n=3); (B) Influence of drug loading on the particle size and PDI (Means ± SD, n=3); (C) influence of lyophilization on the particle size and PDI (Means ± SD, n=3). (D) Fourier transform infrared (FTIR) spectra of BIC and NS formulation; (E) Differential scanning calorimetry thermograms of the powder samples of BIC, BIC NS, and physical mixture.

- The percentage of height reduction of MNs was less than 10%, which suggests the MNs were strong enough to bear a fore of 32N. (Figure I)
- The insertion depth into Parafilm M®, a skin simulant, was up to 504 µm (Figure G and H)
- Compared with drug powder-loaded MNs, it was found that 267.02 ± 45.81 mg drug was deposited from NS-loaded MNs after 24 h. (Figure J and K)

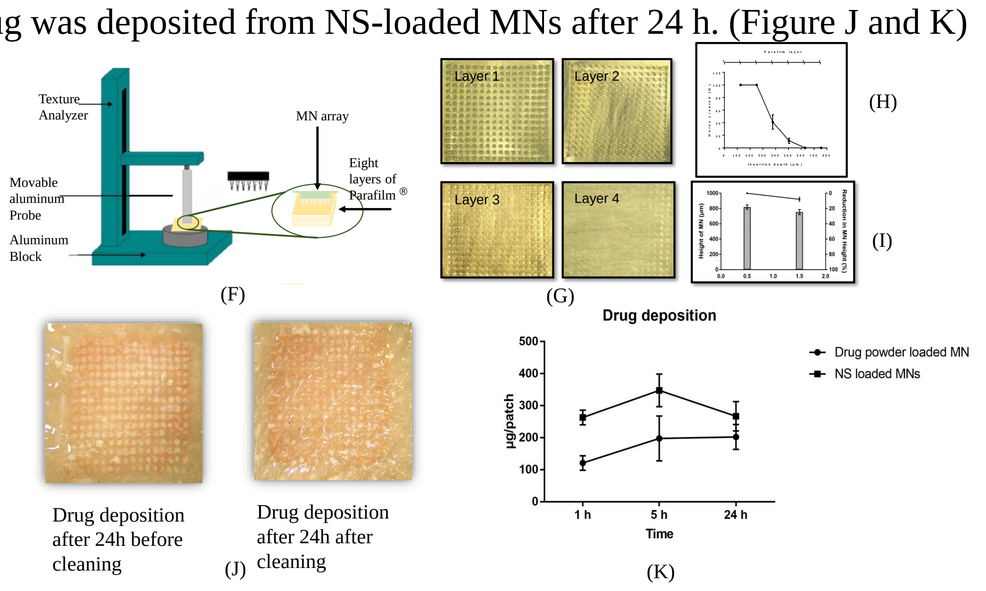

Figure 4. (F) Schematic representation of the Texture Analyser setup used to investigate the Parafilm® insertion; (G and H) Images of different layers of Parafilm®; (I) Percentage reduction in height of MNs upon exertion of a force of 32 N (Means ± SD， n=3); (J) Images of drug deposition from MNs after 24 h; (K) Drug deposition of the NS-loaded MNs from the time point of 1 h, 5 h and 24 h.

Conclusions

The BIC NS was successfully fabricated using wet-media milling method in laboratory scale and characterized. The NS-loaded MN patches were prepared and characterised, revealing favorable mechanical strength and insertion behavior. In future studies, *ex vivo* dermatokinetic study, skin distribution, as well as in vivo pharmacokinetics will be explored.

References

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