Effect of Microneedle Treatment on the *In-vitro* Skin Permeation of Vismodegib

Hiep X. Nguyen, Ajay K. Banga
Mercer University College of Pharmacy, Atlanta, GA 30341

INTRODUCTION

Vismodegib (MW 421.3; log P 2.7) was approved by FDA in January 2012 to treat advanced basal cell carcinoma. Phase I clinical trials proved that vismodegib effectively treated locally advanced or solid tumor with only minor side effects [1]. Microneedles can be used to overcome the rate liming barrier for skin delivery, allowing the drug to diffuse through the micropores created on skin [2]. This project investigated the in-vitro delivery of vismodegib across dermatomed porcine ear skin mounted on Franz diffusion cells.

METHODOLOGY

Donor solution (100 µL) consisted of vismodegib 7 mg/mL dissolved in propylene glycol. Receptor chamber was filled with 10 mM phosphate buffer: polyethylene glycol 400 (50:50 v/v) to maintain sink conditions. Samples were taken at 0h, 1h, 2h, 4h, 6h, 8h, 10h, 22h, 24h and analyzed using a gradient reverse-phase high-performance liquid chromatography method. Maltose microneedles were 500 µm long and were stacked in 3 layers. Metal microneedle array is either 1200 µm long or 1500 µm long (AdminPen TM).

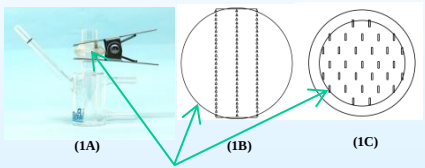

Figure 1. *In-vitro* Permeation Study by vertical Franz diffusion cell (1A) Franz cell; (1B) Maltose microneedle array on permeation area; (1C) Metal microneedle array on permeation area

RESULTS

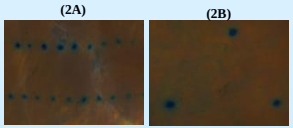

Figure 2. Maltose (2A) and metal (2B) microneedles successfully created microchannels in skin by methylene blue staining. The micropores distribution followed the microneedles pattern on array.

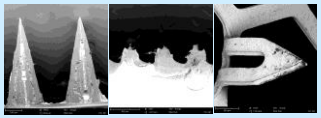

Figure 3. SEM Images of (3A, 3B) maltose and (3C) metal 1200 microneedles. As the treatment duration increased from 1 min to 2 min, maltose microneedles length decreased.

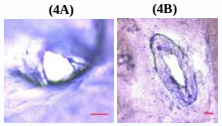

Figure 4. Micropores made by maltose (4A), metal 1200 (4B) microneedle. The shape of the pores followed the geometry of microneedles.

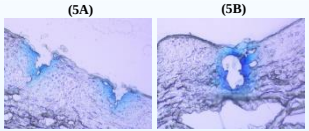

Figure 5. Microscopic images of histological sectioning by maltose (5A), metal 1500 (5B) microneedle.

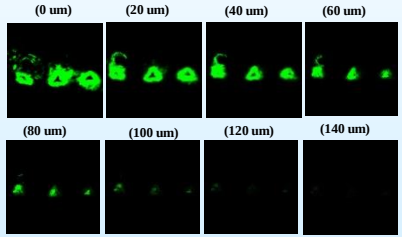

Figure 6. Confocal microscopy with 0.2 µm sized FluoSpheres® to study the depth of the created channels. Permeation pattern indicated depth of microchannels to be 140 ± 10 µm for maltose microneedles.

Delivery through dermatomed pig ear skin (1.11 ± 0.67 µg/sq.cm) was increased when the skin was treated with maltose microneedles (5.42 ± 4.4 µg/sq.cm). The equilibration time for skin after mounting on Franz cells was also found to affect delivery significantly. Delivery was much higher when the skin was not equilibrated, suggesting that micropores close over time when the skin hydrates. This was supported by measurements of transepidermal water loss which was found to decrease with increasing skin hydration. Admin metal microneedles were also tested and delivery was higher (39.8 ± 33.6 µg/sq.cm) with 1500 µm long needles as compared to 1200 µm long needles (26.0 ± 36.12 µg/sq.cm), though high variation in data was observed.

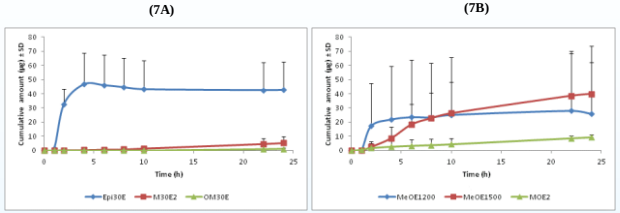

Figure 7. Epidermis allowed more drug to penetrate than dermatomed skin with and without maltose microneedles (7A). Maltose, metal 1200, metal 1500 microneedles did not give a significantly different permeation profile (7B).

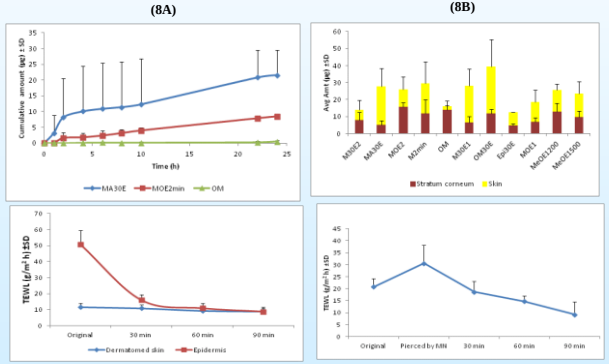

Figure 8. Maltose microneedles treatment after 30-min equilibration facilitated vismodegib delivery through dermatomed porcine ear skin (8A). Fig. 8B illustrated the amount of Vismodegib in skin.

Figure 9. TEWL increased after microneedle treatment, but decreased after that because the skin surface got dry and the micropores closed

CONCLUSIONS

Vismodegib was delivered across dermatomed porcine ear skin and delivery was enhanced by microneedles and affected by the skin equilibration time.

REFERENCES

[1]. De Smaele E, Erretti E, Gulino A., "Vismodegib, a small-molecule inhibitor of the hedgehog pathway for the treatment of advanced cancers", *Curr Opin Investig Drugs*, **11**(6), 707-18 (2010).
[2]. Sivamani RK, Stoeber B, Liepmann D, Maibach HI, "Microneedle penetration and Injection past the stratum corneum in humans", *J Dermatolog Treat*, **20**(3), 156-9 (2009).