W5079

ENHANCED DELIVERY OF VISMODEGIB BY MICRONEEDLE TREATMENT: EFFECT OF NEEDLE LENGTH, EQUILIBRATION TIME AND TREATMENT DURATION

HIEP X. NGUYEN and AJAY K. BANGA

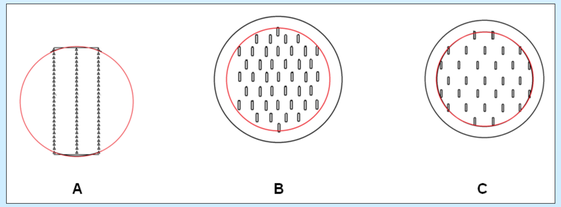
Mercer University College of Pharmacy, Department of Pharmaceutical Sciences, Atlanta, GA 30341

PURPOSE

The study investigated the effect of microneedle treatment (Maltose microneedles, Admin Pen ™ 1200 and Admin Pen ™ 1500) on *in vitro* transdermal delivery of vismodegib with different needle lengths (500; 1100; 1400 µm), skin equilibration time (0; 30 minutes) and microneedle insertion duration (1; 2; 4 minutes).

METHODS

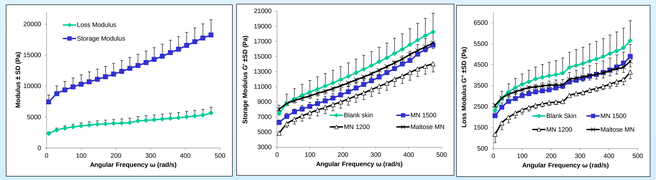
- The microneedle shape, dimension, surface morphology and distribution pattern on array by Phenom ™ field emission SEM system.
- Dynamic viscoelasticity of porcine ear skin by an oscillatory rheometer.
- The formation of microchannels on skin by dye binding studies (Proscope HR microscope), histology studies (Microm HM505E).
- The depth and surface area of microchannels by a computerized Leica SP 8 confocal laser microscope.
- The pore uniformity and relative flux values by calcein imaging studies.
- The barrier integrity and humidity of skin by transepidermal water loss (TEWL) measurement.
- The rate and extent of drug transported across skin and drug retention in skin by *In vitro* permeation studies using vertical Franz diffusion cells.
- The *In vitro* EpiDerm™ skin irritation test of vismodegib solution in PG 7 mg/mL by 3D *in vitro* reconstructed human epidermal model EpiDerm.



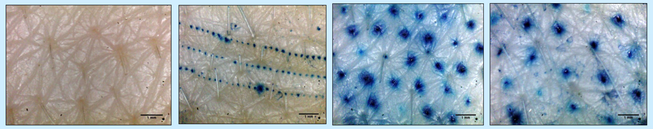
Microneedle array on the *in vitro* diffusion area (0.64 cm^2-Red circle): (A) 81 Maltose microneedles, (B) 43 Admin Pen™ 1200 microneedles, (C) 31 Admin Pen™ 1500 microneedles

RESULTS

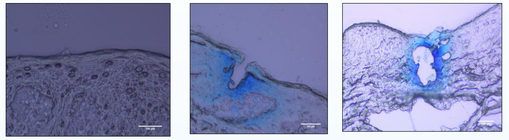
Microneedle dimensions (µm)		*SEM image magnification*	*Maltose microneedles*	*Admin Pen™ 1200*	*Admin Pen™ 1500*
Height (n=10)		400X	505.90 ± 9.54		
		200X		1108.30 ± 21.81	1396 ± 8.89
Base	Shape		Equilateral triangle	Rectangle	Rectangle
	Dimensions (n=10)	400X	223.70 ± 13.16		
		200X		456.20 ± 9.58 (long) 89.80 ± 6.39 (wide)	562.90 ± 9.00 (long) 120.40 ± 9.28 (wide)
Tip-to-tip distance (n=10)		400X	353.30 ± 13.82		
		100X		1638.60 ± 10.15	2010.70 ± 12.68



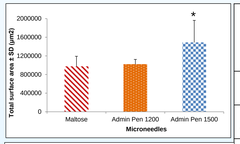
Skin samples were predominantly elastic, less resistant after microneedle treatment



Microchannels were created successfully in dermatomed porcine ear skin: Blank skin, Maltose microneedle, Admin Pen™ 1200, Admin Pen™ 1500



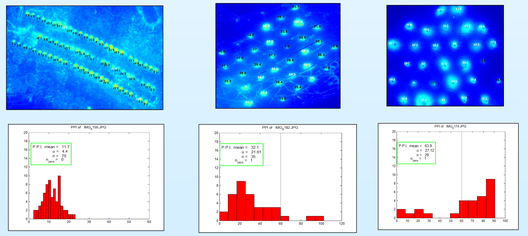
Histological sectioning images of skin samples treated with (A) Blank skin, (B) Maltose microneedles, (C) Admin Pen™ 1500



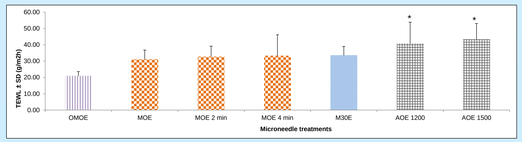
* indicated statistical difference from other group (One-Way ANOVA, *p* value < 0.05)

Microneedles	*Depth of channels (µm) (n=10)*
Maltose MN	140.5 ± 10.12
Admin Pen™ 1200	242.5 ± 22.27
Admin Pen™ 1500	278 ± 33.35

The total surface area and average depth of microchannels. An increase in needle length enhanced the depth of the channels

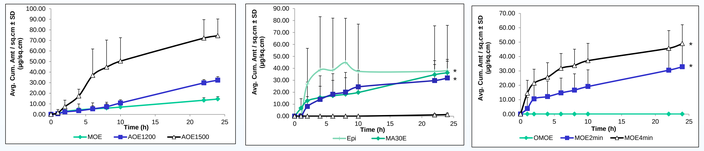


The microchannels with Pore Permeability Index values and histogram of Maltose MN, Admin Pen™ 1200 and Admin Pen™ 1500



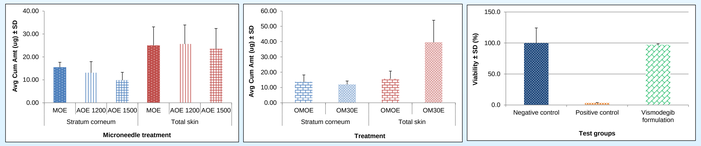
* indicated statistical difference from OMOE group (One-Way ANOVA, *p* value < 0.05)

Transepidermal water loss values of skin treated by microneedles



In vitro permeability of vismodegib through microneedle-treated porcine ear skin
Maltose MN (MOE), Admin Pen™ 1200 (AOE1200), Admin Pen™ 1500 (AOE1500)
MOE2min (2-min treatment), MOE4min (4-min treatment),
M30E (30-min equilibration), MOE (No equilibration), OM (No treatment) (n=4)

Microneedles significantly enhanced vismodegib permeability through skin. Maltose MN delivered a statistically significant smaller amount of drug to the skin than Admin Pen™ 1200, Admin Pen™ 1500. The 30-min post-MN treatment equilibration time enhanced the drug delivery. A positive correlation between MN treatment duration and the drug delivery.



The amount of drug in skin layers: MOE, AOE 1200, AOE 1500, OMOE, OM30E (30-min equilibration increased the amount of drug in skin) and skin irritation test: Vismodegib solution in PG (7mg/ml) was non-irritant (NI) (Relative tissue viability: 97.1 ± 1.44 %).

CONCLUSIONS

Changes in microneedle length, equilibration time and treatment duration altered vismodegib transdermal delivery.

REFERENCES

1. Macha MA, Batra SK, Ganti AK. Profile of vismodegib and its potential in the treatment of advanced basal cell carcinoma. Cancer Manag Res. 2013;5:197-203.
2. Kolli CS, Banga AK. Characterization of solid maltose microneedles and their use for transdermal delivery. Pharm Res. 2008;25(1):104-113.
3. Gomaa YA, El-Khordagui LK, Garland MJ, Donnelly RF, McInnes F, Meidan VM. Effect of microneedle treatment on the skin permeation of a nanoencapsulated dye. J Pharm Pharmacol. 2012; 64(11):1592-1602.