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Development of a Sustained Transdermal Delivery System of Amloride for Management of Resistant Hypertension

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Development of a Sustained Transdermal Delivery System of Amiloride for Management of Resistant Hypertension

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Introduction



- About ~ 76 million adult Americans with hypertension; a prevalence rate of almost 12% would translate into an estimated 9 million Americans with **resistant hypertension**.

Resistant hypertension is a condition in which blood pressure remains above the ideal value (120/80 mmHg), despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses.

Amiloride

- Diuretic medication added to the treatment regimen is suitable for the treatment of resistant hypertension.

Current Drug Delivery Oral delivery:
5mg of tablet /1x daily

Microneedle-Based Transdermal Delivery

Limitations

- Low oral bioavailability.
- Poor patient compliance to multi-drug treatment regimen.
- Gastrointestinal side effects

- Improved bioavailability
- Sustained therapeutic effect with controlled drug release.
- Patient compliance

Objectives

Explore and investigate transdermal strategies for amiloride permeation through skin.

Methods

1. HPLC Method development

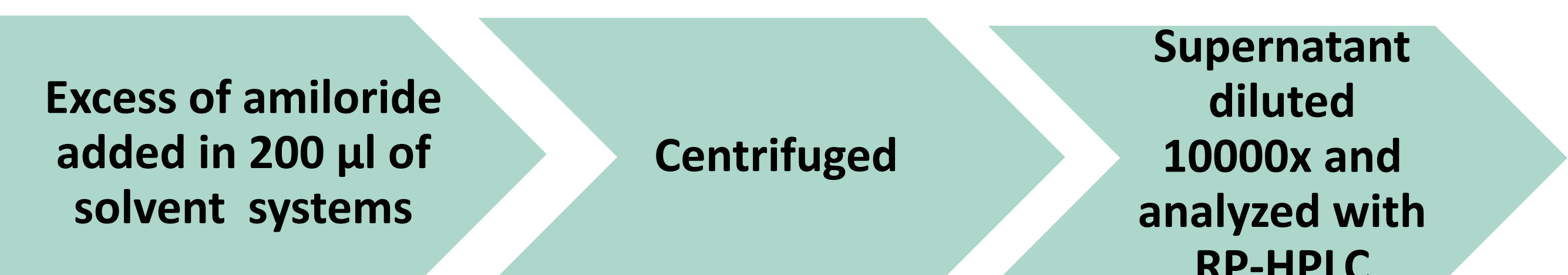
Isocratic elution on Kinetex® 5µm, 100 Å, 250 X 4.6 mm C18 column using 100% mobile phase at a flow rate of 0.8 mL/min, column temperature of 40°C, and UV detection at 360 nm.



Table1: HPLC method parameters

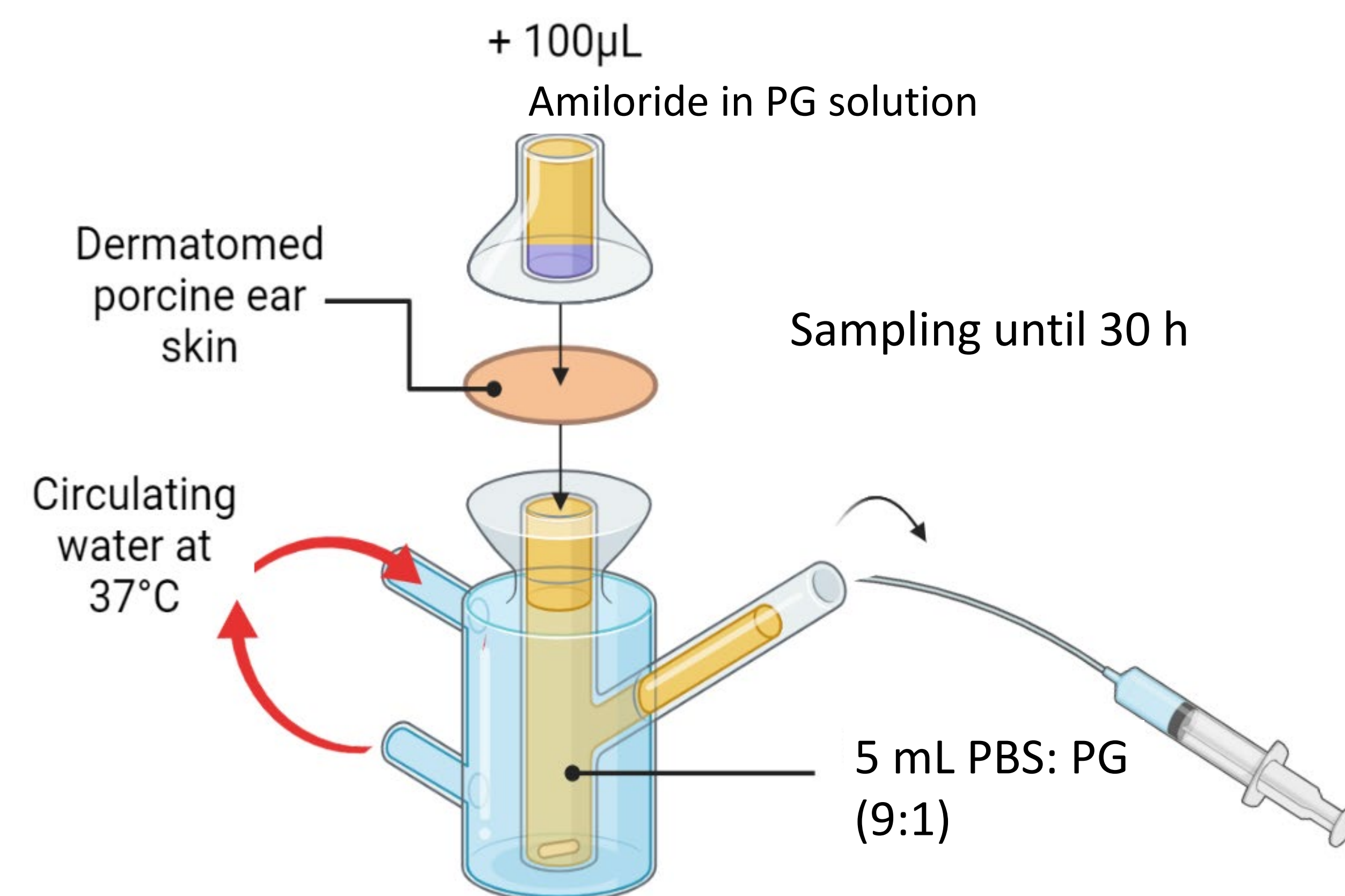
Mobile Phase	pH	Flow rate	Retention time	Injection volume	Wavelength
Acetonitrile 12% (glacial acetic acid 0.4%)	4.5	0.8 mL/min	4.5 min	45 µL	360 nm

2. Solubility Study of amiloride in different solvent systems



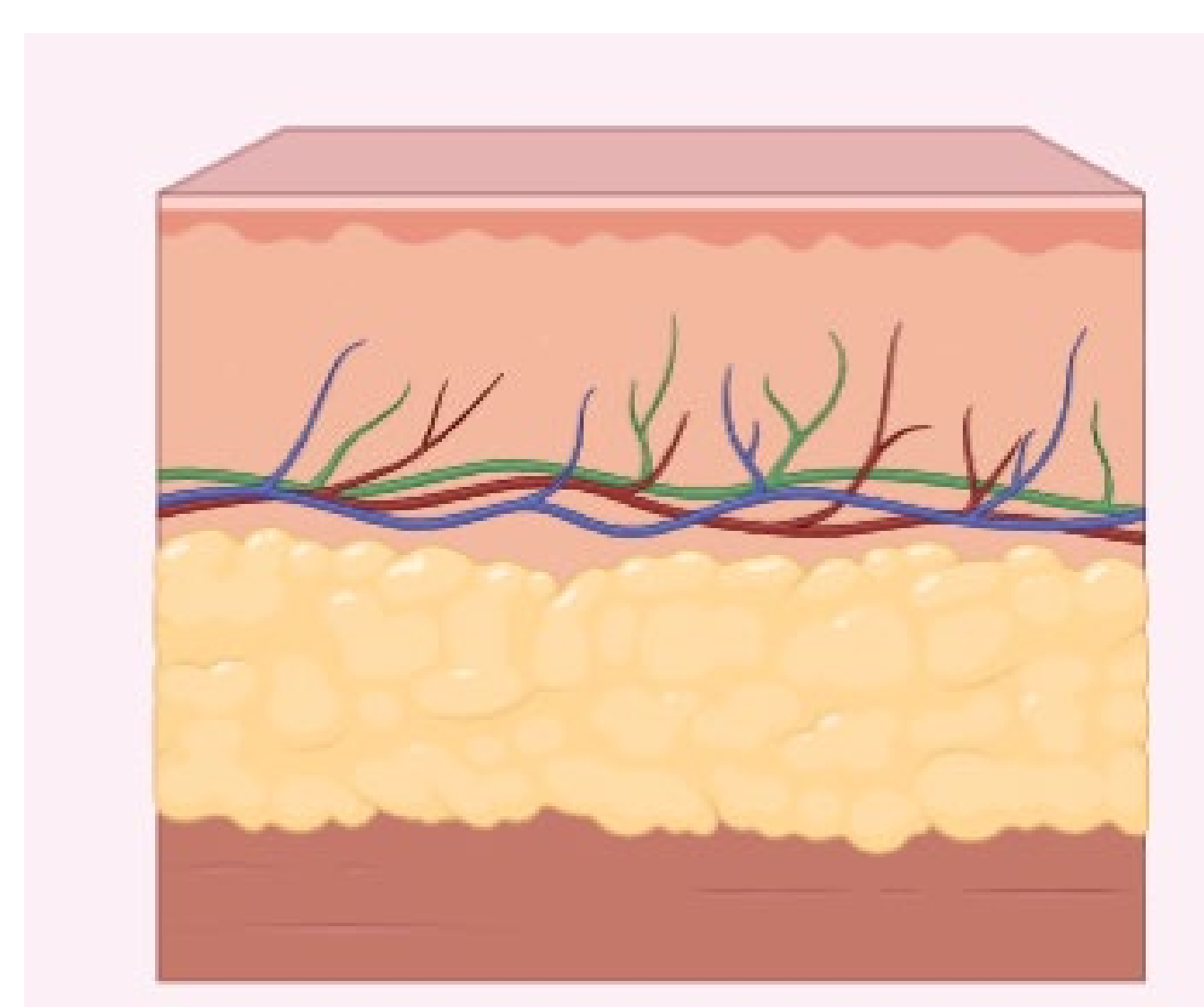
Methods Contd...

3: In vitro permeation of amiloride across intact and microneedle-treated porcine ear skin was evaluated using Franz Diffusion cells over 30h. The optimized reverse-phase HPLC analysis carried out.



Passive permeation

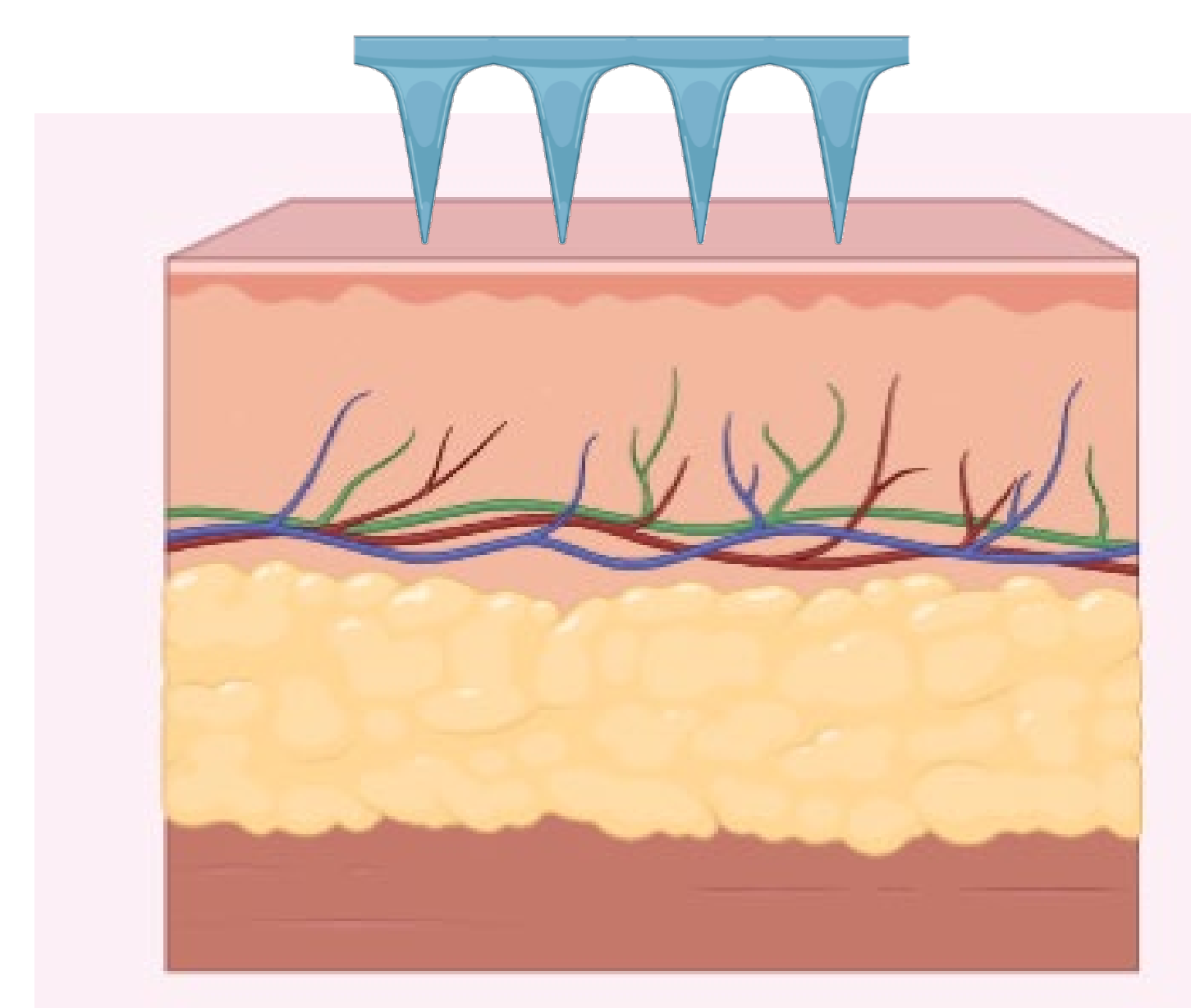
INTACT SKIN



Active permeation

MICRONEEDLE-TREATED

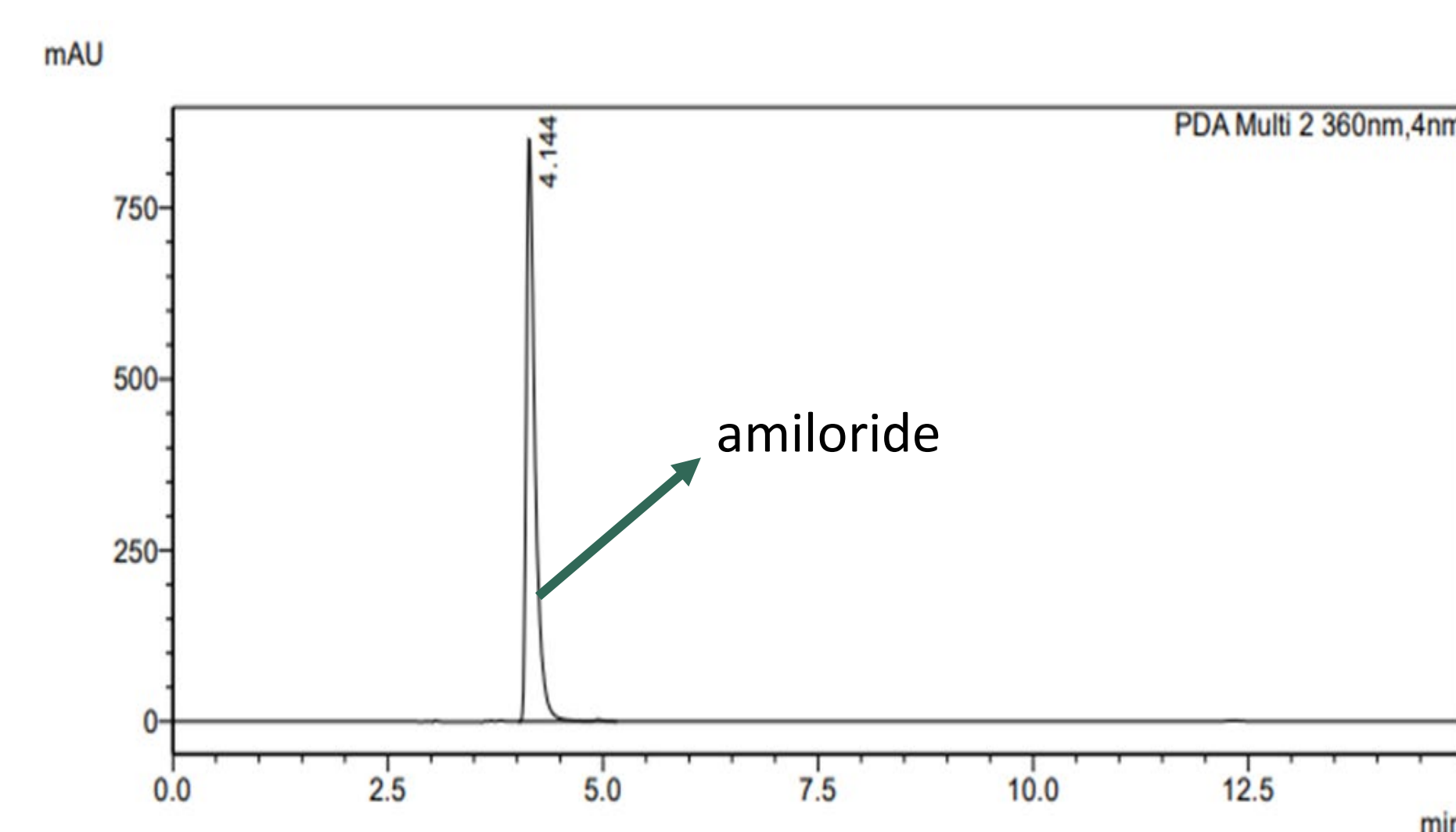
36 needle array inserted at a speed of 13,000 insertions/min into skin



Results

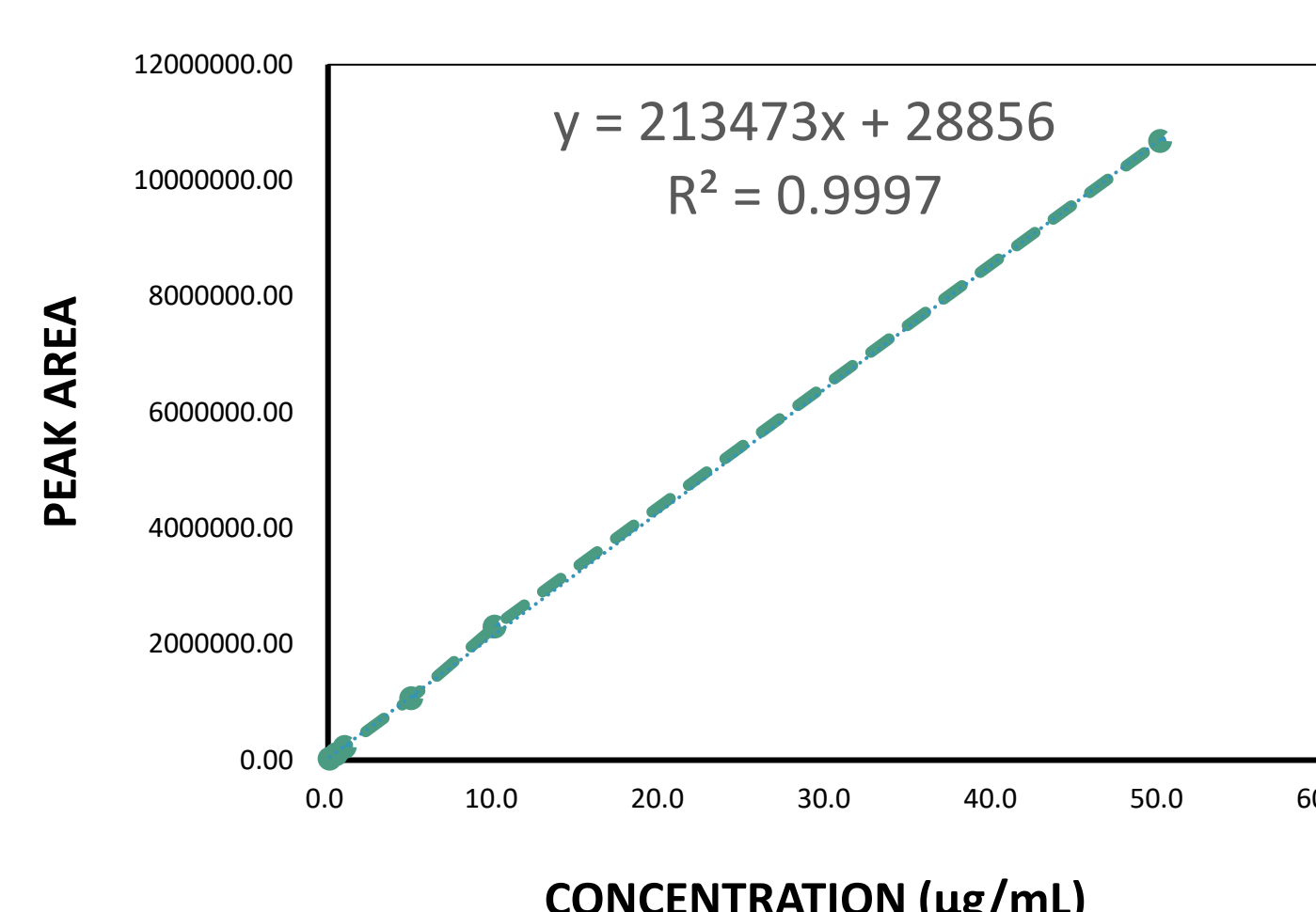
HPLC METHOD:

DRUG PEAK CHROMATOGRAM at 360 nm



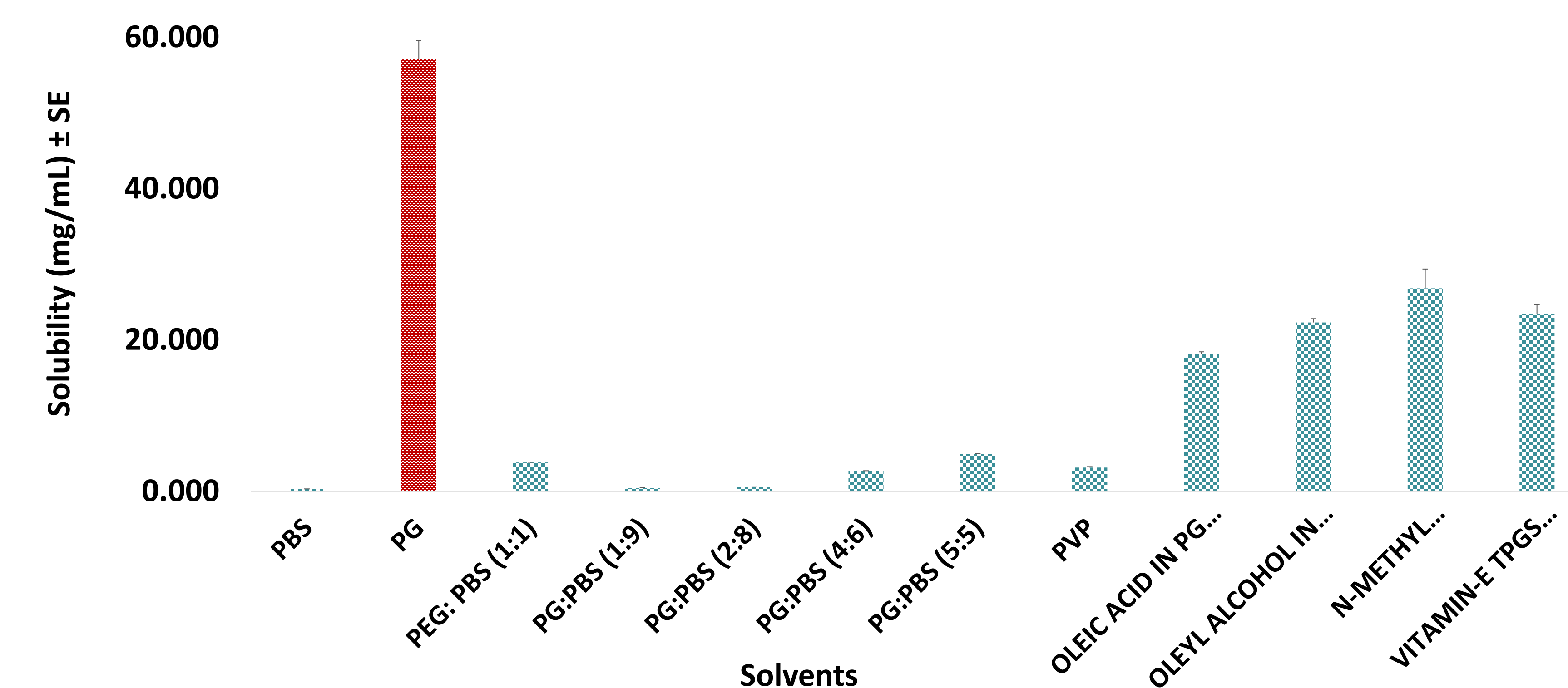
Chromatogram view of drug with retention time of ~ 4.5 min

CALIBRATION PLOT

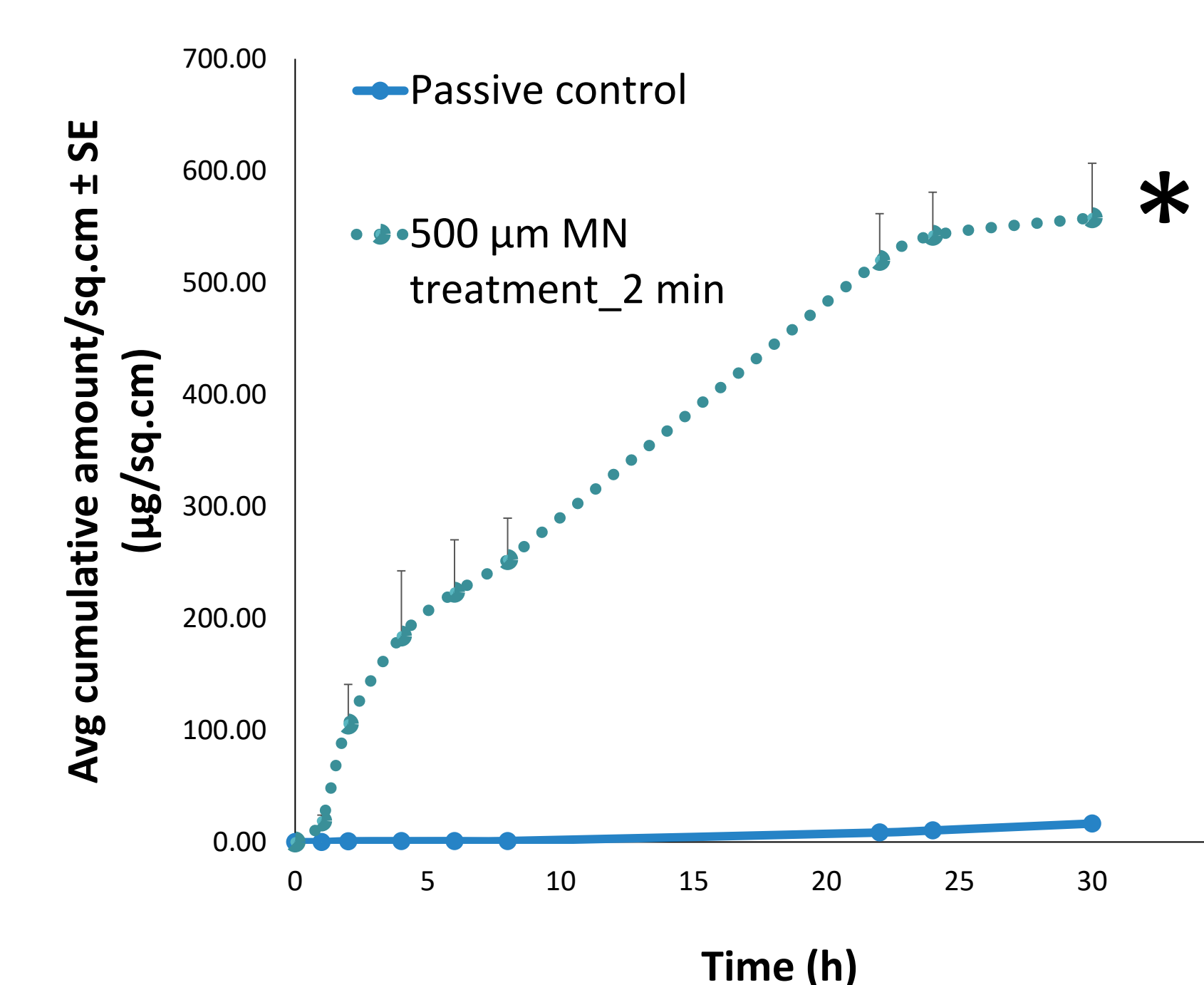


Results Contd..

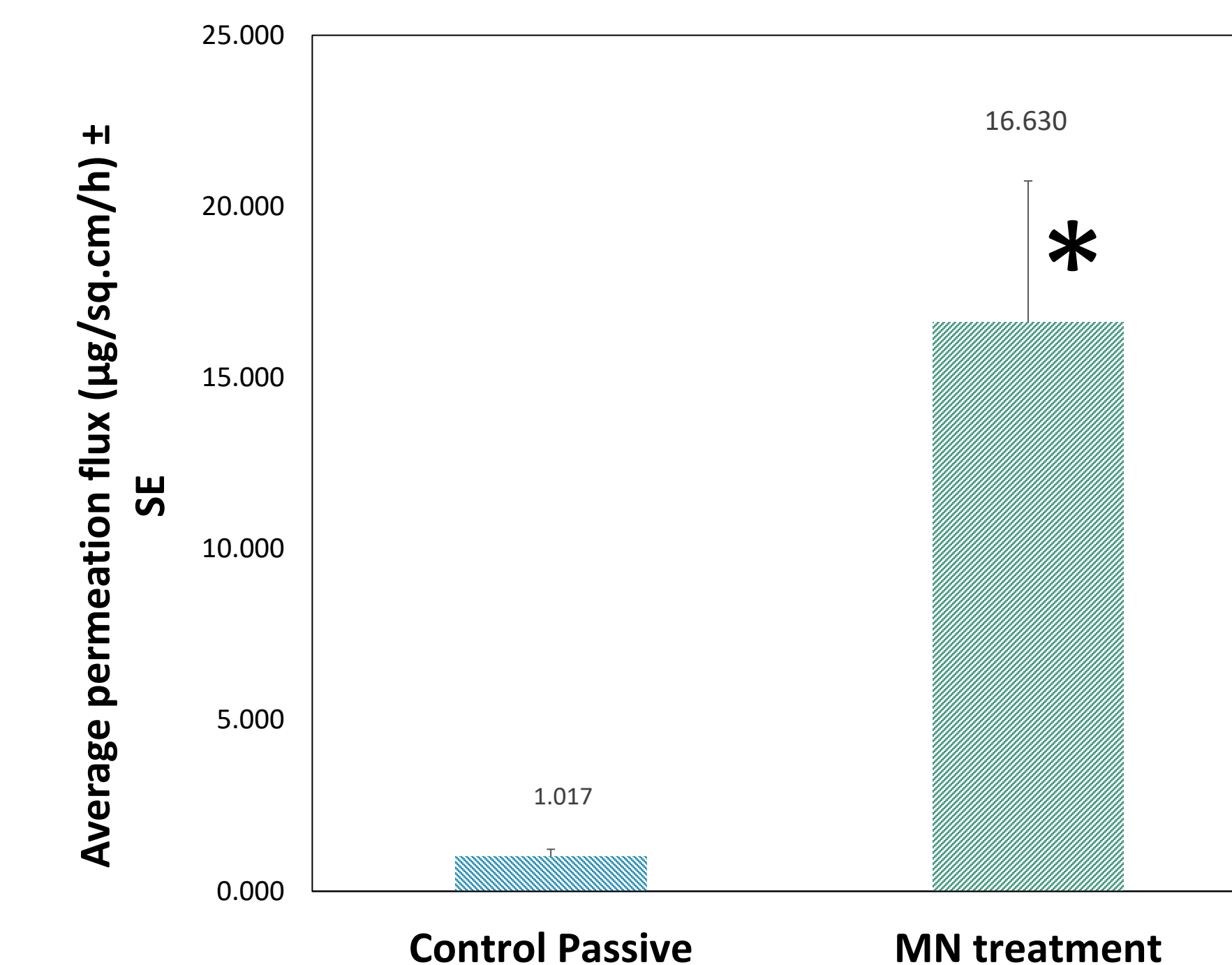
SOLUBILITY SCREENING



Amiloride is most soluble in propylene glycol (57.18 ± 2.41 mg/mL) with least solubility in phosphate buffer saline (0.311 ± 0.004 mg/mL)



In vitro skin permeation of amiloride across intact and microporated skin. The amount of amiloride permeation after 30 h was 557.92 ± 48.77 µg/cm² across microporated skin which was significantly higher than the control (p<0.05, Student's t test denoted by *)



Steady state permeation flux showing passive control and microneedle treated skin, with **MN significantly higher than the control group** (16.63 ± 4.12 µg/cm²/h, p<0.05, Student's t test denoted by *)

References

- Puri A, Frempong D, Mishra D, Dogra P. Microneedle-mediated transdermal delivery of naloxone hydrochloride for treatment of opioid overdose. International Journal of Pharmaceutics. Elsevier B.V.; 2021;604:120739.
- Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation. 2012 Apr 3; 125 (13):1594-6. doi: 10.1161/CIRCULATIONAHA.112.097345. Epub 2012 Feb 29. PMID: 22379111; PMCID: PMC3350774.

Conclusions

Microneedles were found to significantly enhance the permeation flux of amiloride by 16 folds as compared to the control intact skin (p<0.05). The feasibility of developing a sustained microneedle-mediated transdermal delivery system of amiloride was thus, demonstrated.