Poster#481

Microneedles for rapid and sustained delivery of acetaminophen and caffeine for migraine therapy

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Introduction

- Conventional migraine treatments are often delayed and inefficient.
- Oral medications can be ineffective due to nausea and vomiting, and injectables are not preferred by many patients. Microneedle (MN) delivery of caffeine (CAF) and acetaminophen (ACM) offers a patient-friendly solution for rapid and sustained relief.

Objective

- This study aims to develop a dissolving MN (dMN) patch for rapid and sustained delivery of ACM and CAF.
- in these studies, solid MNs will be used as proof of concept to quantify the effect of MN treatment on skin permeation of ACM and CAF from topical gel.

Method

dMN preparation and characterization

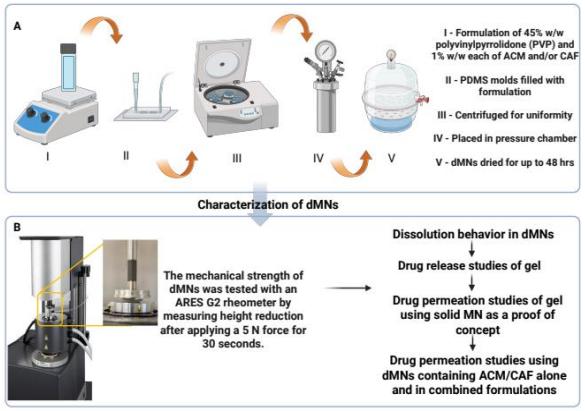

Fig 1: A) Preparation of dMNs, B) ARES G2 rheometer used for axial compression testing

In vitro drug release study

- Diffusion cells: Static Franz diffusion cells (Permegear, USA), 20 mL receptor volume with 4.91 cm^2 diffusion area
- Membrane: SnakeSkin™ dialysis tubing, 10,000 MWCO
- Receiver medium: HEPES buffer, pH 7.4, warmed to 37 °C
- Study duration: 8 hours

Fig 2: A) 45% PVP gel loaded with 1% each ACM and CAF, B) Static Franz diffusion cells

dMNs permeation studies

- Performed using Franz diffusion cells for both the drugs individually and in combination

In vitro drug permeation study

- Diffusion cells: Flow-through diffusion cells (Permegear, USA) with 1.76 cm^2 diffusion area.
- Membrane: Excised dermatomed porcine skin (~0.8 µm thickness) pretreated with solid MNs (500 µm length)
- Receiver medium: HEPES buffer, pH 7.4, 37 °C with a 25 µL/mL flow rate for 24 hours

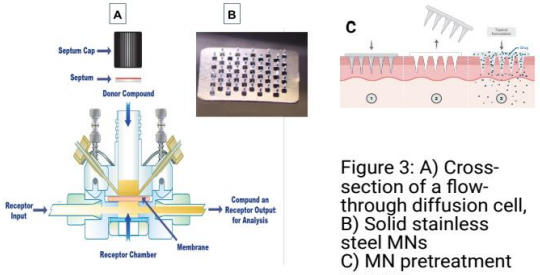

Figure 3: A) Cross-section of a flow-through diffusion cell, B) Solid stainless steel MNs C) MN pretreatment process

Result

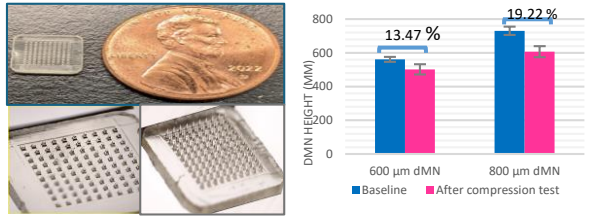

Fig 4: A) dMNs patch containing ACM and CAF B) The dMNs displayed minimal % height reduction after the compression test. Data above bars represent % height reduction (n=6, mean ± SD)

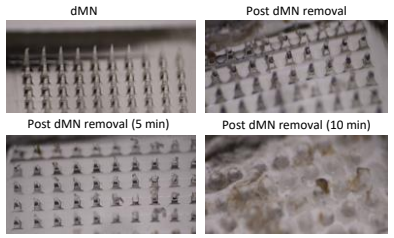

Fig. 6: Microscopic images showing the dissolution behavior of dMNs before and after application

Result

In vitro drug release study

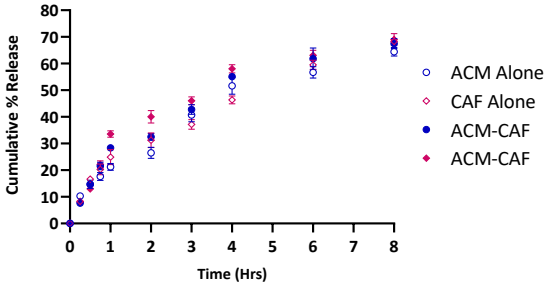

Fig 7: Drug release profiles from 45% w/w PVP gel containing both ACM and CAF (1% w/w) (n=3, mean ± SD)

In vitro drug permeation study

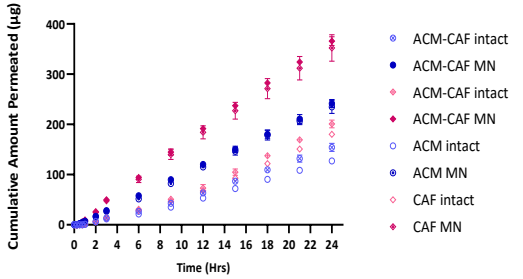

Fig 8: Drug permeation profiles from 45% w/w PVP gel containing both ACM and CAF (1% w/w) applied to MN-treated and intact skin (n=3, mean ± SD). All blue points represent ACM, and all red points represent CAF.

Table 1: Permeation studies data from PVP 45 % gel applied to skin treated with solid MNs

Formulation	Steady-state flux (Jss, µg/cm^2/h) of ACM and CAF when delivered alone or in combination			
	ACM combined	ACM Alone	CAF combined	CAF alone
Intact Skin	4.27 ± 0.2	3.48 ± 0.22	6.05 ± 0.29	5.36±0.13
MN Treated	5.77 ± 0.24	5.55 ± 0.55	8.07 ± 0.80	7.87±0.62

dMNs permeation studies

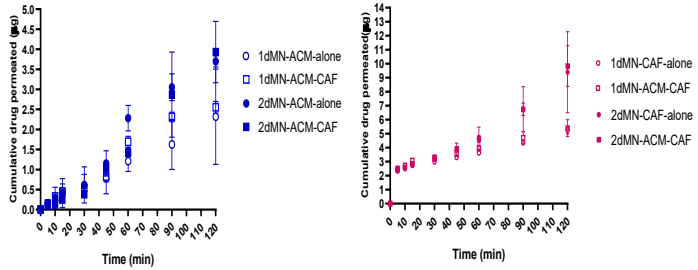

Fig 10: *In vitro* permeation of CAF from dMNs containing CAF alone or ACM + CAF, from 1 dMN (open symbol) vs 2 dMNs (closed symbol) (n=3, mean± SD)

Table 2: Total amount of drug permeated through dMNs (in µg), (n=3, mean± SD)

Formulation	ACM	CAF
1dMN-Alone	2.39 ± 1.19	5.21 ± 0.23
2dMN- Alone	3.70 ± 0.14	9.39 ± 0.28
1dMN- Combined	2.55 ± 0.14	5.39 ± 0.59
2dMN– Combined	3.93 ± 0.76	9.83 ± 0.14

- dMNs enabled faster onset of delivery, with measurable drug concentrations as early as 5 min (vs gels applied to intact skin, which allowed both drugs to be detected at 1 hour).

Conclusions

- Flux increased for ACM (1.33X) and CAF (1.35X) through skin pretreated with solid MN compared to untreated skin in combined formulation.
- dMNs enabled drug detection within just 5 minutes, highlighting their promise for rapid and effective migraine management.
- **Within 120 minutes, 2dMNs demonstrated approximately 1.5× and 1.8× higher total permeation of ACM and CAF, compared to 1 dMNs in combined formulation**

Acknowledgements

Funding Source: This work was funded by NIH R35GM149337.
Brogden lab members: Valeria Cota, Joseph Correa, Brianna Haase, Krishna Kumar Patel

References

- Bentivegna E, Onan D, Martelletti P. Unmet Needs in Preventive Treatment of, Migraine. Neurol 2023;12(2):337–42.
- Yang J, Liu X, Fu Y, Song Y. Recent advances of microneedles for biomedical applications: drug delivery and beyond. Acta Pharm Sin B, 2019;9(3):469–83