Assessing topical drug penetration into the skin using Raman spectroscopy

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PURPOSE

Quantitative evaluation of a topically applied drug's bioavailability (BA) at its site of action in the skin represents an unmet scientific challenge.

Most dermatological drug targets are located in the epidermis/upper dermis, below the stratum corneum (SC), which is the principal barrier to drug absorption.

While some alternatives to clinical assessment exist, identification and validation of surrogate approaches for evaluation of local BA represents a work-in-progress.

OBJECTIVE

The overall objective of this study was to test the hypotheses that spectroscopic (specifically, **Raman**) offers **a non-invasive, accurate, sensitive and reproducible method** to determine the **rate and extent to which a topically administered** drug becomes available at or near its site of action below the SC. The specific aim here was to show that the loss of Raman signal with depth can be corrected using the attenuation of the amide I signal.

METHODS

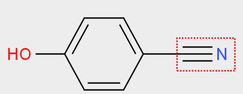
RAMAN SPECTROSCOPY

- Renishaw inVia Raman microscope working in reflection mode.
- Sample illuminated with a pre-calibrated 785 nm (150 mW) laser.
- *Ex vivo* abdominal pig skin on an aluminum support.

Molecule of interest

Cyanophenol (CP) has strong -C≡N Raman signal (2230 cm^{-1}) in a frequency range where skin is spectroscopically 'transparent'.

Cyanophenol



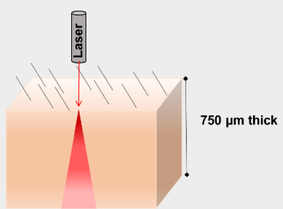
Cyanophenol formulations

1. Saturated solution (**170 mg mL^{-1}**) of CP in **50:50 v/v propylene glycol (PG)-water**;
2. 25% saturated solution (**42.5 mg mL^{-1}**) of CP in **50:50 v/v PG-water;**
3. Saturated solution (**17 mg mL^{-1}**) of CP in **10:90 v/v PG-water**.

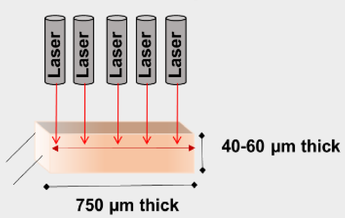
The saturated CP formulations (300 µL) were applied to the skin surface for 1 or 2 hr under occlusion (Parafilm). The fully and 25% saturated 50:50 v/v PG-water formulations were applied for 6 hr in the same way.

After each experiment, the skin was cleaned and cut into small pieces and CP disposition was assessed as functions of depth and time using Raman. Measurements (n = 6) were made either **"top-down"** or in **"cross-section"**.

"Top-down" experiments



Cross-section experiments

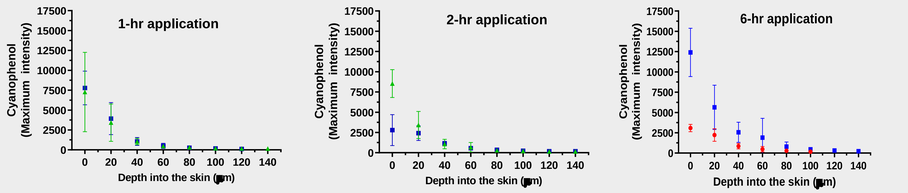


RESULTS

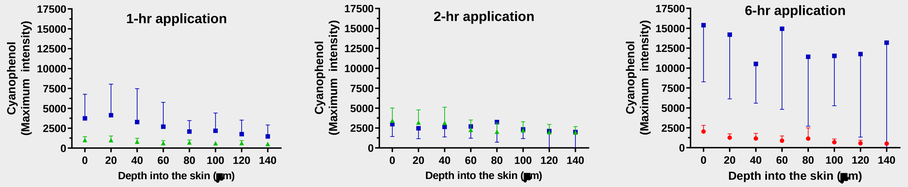
■ Saturated CP (170 mg mL^{-1}) in 50:50 v/v PG-water ● 25% saturated CP (42.5 mg mL^{-1}) in 50:50 v/v PG-water

▲ Saturated CP (17 mg mL^{-1}) in 10:90 v/v PG-water

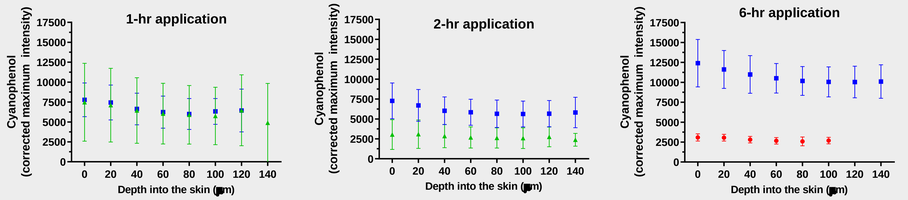
"Top-down" experiments



Cross-section experiments



Correction for signal attenuation



Attenuation with increasing depth of the CP signal in the "top-down" experiments was corrected using the Amide I intensity (from keratin) at 1650 cm^{-1}. The approximately constant CP concentration with depth is expected because there is no flux from the inner skin surface during uptake and the lag time for CP is ~0.5 h.

CONCLUSIONS

- Two saturated CP formulations produced very similar profiles across the skin; when the degree of saturation was reduced to 25%, the profile was adjusted proportionally.
- Overall, Raman spectroscopy was able to track drug penetration as a function of depth into the skin (and beyond the SC). Therefore, Raman spectroscopy has the potential to evaluate drug bioavailability in the skin from different formulations.
- Signal attenuation by absorption/scattering of radiation can be mitigated by normalization with the Amide I intensity, which is constant with depth.
- Applying the correction to the "top-down" data aligns the results more closely to the depth profile of the CP signal measured in the "cross-section" experiments.

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