Evaluating Topical Drug Bioavailability in the Skin Using Raman Spectroscopy

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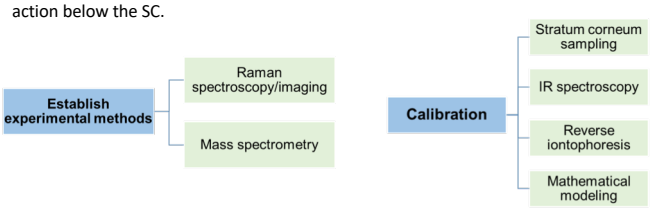
RESEARCH STRATEGY

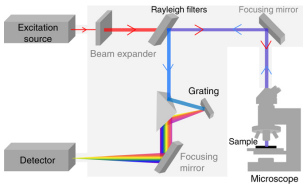
- Quantitative evaluation of a topically applied drug's bioavailability (BA) at its site of action in the skin represents an unmet scientific challenge.
- Most dermatological drug targets are located in the epidermis/upper dermis, below the stratum corneum (SC = principal barrier).
- While a few alternatives to clinical assessment exist, identification and validation of surrogate approaches to evaluate of local BA represents a work-in-progress.
- Central hypothesis: That spectroscopic (specifically, Raman) imaging 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.



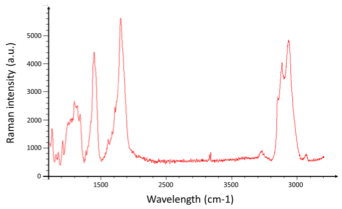
RAMAN SPECTROSCOPY

- Renishaw inVia Raman microscope working in reflection mode.
- Sample illuminated with a pre-calibrated 785 nm (100 mW) laser.
- *Ex vivo* abdominal pig skin on an aluminum support.

Raman spectroscopy principle

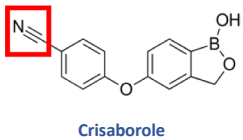


Raman spectrum of pig skin (532 nm)

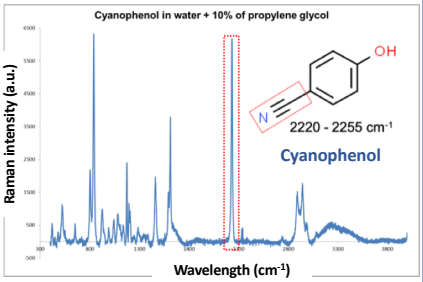


MOLECULES OF INTEREST

Crisaborole and cyanophenol (CP) have strong -C≡N Raman signals in a frequency range where skin is spectroscopically 'transparent'.

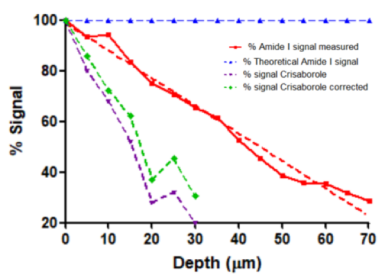


Crisaborole



CORRECTION FOR SIGNAL ATTENUATION

Signal attenuation from drug as a function of depth into skin is corrected using the Amide I signal at 1650 cm^{-1} (either the actual data points – solid red curve – or the linear fit – dashed red line).

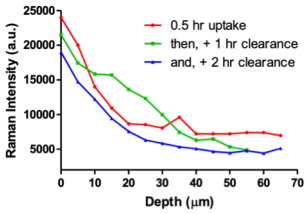


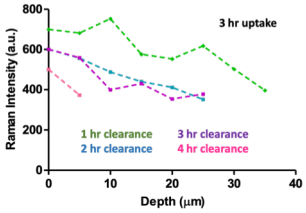
Example of crisaborole signal correction using the Amide I 'normalization'.

Drug applied for 3 hr, formulation removed and spectra acquired 3 hr later.

TRACKING DRUG CLEARANCE FROM SC

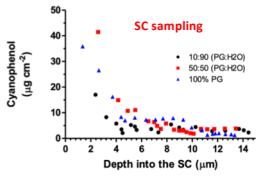
- CP (17.5 mg/mL) in 10:90 v/v propylene glycol (PG)-water.
- After 0.5 hr application, skin surface cleaned and Raman measurements recorded.
- CP clearance from skin determined at 1 and 2 hr following removal of formulation.
- Crisaborole (5.9 mg/mL) in 70:30 v/v propylene glycol (PG)-water.
- After 3 hr application, skin surface cleaned and Raman profile assessed.
- Clearance of drug from skin then recorded at 1, 2, 3 and 4 hr following removal of formulation.

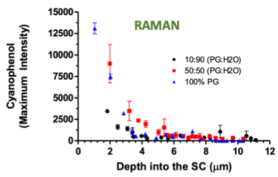




COMPARING FORMULATIONS

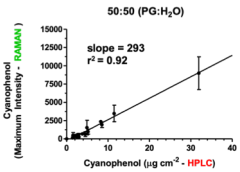
Three formulations of 4-CP (saturated solutions in pure PG, 50:50 v/v PG/water and 10:90 v/v PG/water) were applied to porcine skin *ex vivo* for 1 hour and uptake into the SC was assessed by tape-stripping and by Raman spectroscopy.

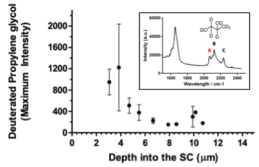




Overlap between the results was self-evident, with high correlations between Raman signal intensity and CP measured in the SC (illustrated for the 50:50 formulation below).

Data have also been acquired, for example, tracking an excipient penetrating into skin (shown for deuterated propylene glycol below).





CONCLUSIONS

Raman spectroscopy is able to: [1] track drug penetration as a function of depth into the skin (and beyond the SC), and [2] track drug clearance from the SC.

Furthermore, the approach has the potential to compare drug delivery into skin from different formulations, and to follow the penetration of certain formulation excipients.

Artifacts due to signal attenuation by absorption/scattering of radiation can be mitigated by normalization, and correlation with complementary techniques (e.g., SC sampling) may offer the opportunity for at least semi-quantification of drug BA using the Raman approach.

ACKNOWLEDGMENTS

This research was supported by the U.S. Department of Health & Human Services, Food & Drug Administration (1-U01- FD006508 and 1-U01-FD004947). The views expressed in this poster do not reflect the official policies of the U.S. Food & Drug Administration or the U.S. Department of Health & Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. We thank Drs. Priyanka Ghosh, Markham Luke and Sam Raney for their valuable input to this work.

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